Interventions for sleep problems during pregnancy: a systematic review

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Conflicts of interest

All authors report no competing interests.

Summary

Sleep problems during pregnancy are prevalent and could be linked to negative outcomes during pregnancy or post-partum. However, these complaints are often underdiagnosed and undertreated. This review aimed to systematically assess the effectiveness of different interventions to ameliorate poor sleep quality and insomnia during pregnancy.

Pubmed, PsycINFO and Medline databases were systematically searched without publication period restriction until 3rd May 2019. Eligible studies had to: include pregnant women of any age and gestational age; use clinical intervention designs targeted at improving sleep outcome; report pre- and post- treatment data for one or more sleep-related outcomes; be published in English, Italian, German, Spanish, or French.

Sixteen studies were selected including 1252 expecting mothers. Studies evaluated the efficacy of various interventions: cognitive behavioral interventions for insomnia (4); pharmacotherapy (1); acupuncture (1); mindfulness and yoga (3); relaxation (5) and herbal medication (2). Only six were randomized controlled trials, and only four evaluated longitudinal outcomes. Preliminary support was found for all interventions, but our knowledge is still too limited by lack of evidence.

There is an utmost urgency to perform high-quality randomized controlled trials for insomnia interventions during pregnancy and to implement effective programs in standard gynecological care.

Abbreviations:

CBT, cognitive behavioral therapy;

CBT-I, cognitive behavioral therapy for insomnia;

MMT, mindfulness mom training;

PICOS, population, intervention, comparison, outcomes and study design;

PRISMA, preferred reporting items for systematic reviews and meta-analyses;

PSQI, pittsburgh sleep quality index;

RCT, randomized controlled trial;

SD, standard deviations;

SE, standard errors;

SIP-AP, sleep improvement protocol from antepartum patients;

TAU, treatment as usual.

Introduction

Sleep is crucial for life, occupying up to a third of the human life span. Poor sleep, either in duration, continuity, or quality, is linked with increased risk for negative health outcomes such as cardiovascular disease, diabetes, depression and anxiety [1-4]. Sleep is an important regulatory psychophysiological process influencing emotion regulation and impulsive behavior [5, 6], which are key mediators of stress adjustment [7]. Insomnia disorder is among the most common complaints in medical practice [8] and it is associated with high direct and indirect costs [9].

Specifically, during pregnancy, women experience sleep disturbances which increase the risk of developing insomnia [10]. The National Sleep Foundation's Women and Sleep Survey in 2007 found that up to 78% of women complained about disturbed sleep during the third trimester of pregnancy [11]. However, pregnant women experience alterations in sleep duration [12, 13], quality [14, 15] and pattern [15-17] across all gestational weeks, and not only during late pregnancy [e.g. 18].

Poor sleep quality during pregnancy has been found to be a prospective risk factor for depression during the prenatal and postpartum period [19-21]. Supporting these data, recent studies showed that sleep disturbances are associated with adverse pregnancy outcomes including intrauterine growth restriction (poor growth of fetus while in the mother's womb during pregnancy), preterm birth, higher risk of cesarean birth and longer labor [22-24]. Psychosocial factors as low socio-economic status, problematic work situation, low educational level, lacking access to prenatal care, drug abuse and conflicts with the partner all contribute to stress during pregnancy [25]. Evidence has shown that a poor sleep quality may be also related to high-levels of experienced stress, and that both are associated with immunological and endocrinological problems, as well as higher morbidity risk [26]. Sleep is likely both an outcome and a predictor of increased levels of stress during pregnancy, which may be linked to a cascade of negative consequences for the birth, the mother and the child.

Nevertheless, there is a tendency to routinely exclude pregnant women from clinical trials evaluating interventions for sleep problems and insomnia [27] and a tendency for mothers to commonly report sleep problems late in pregnancy, even though the problems often started already during the first trimester [15], making women who could benefit from the treatment ineligible [28]. This could lead to underdiagnoses and under-treatment of insomnia and sleep complaints during pregnancy, consistently with what happens for maternal mental health in general [e.g. 29, 30]. Furthermore, it is likely related to a hesitancy to prescribe hypnotic and psychotropic medication to expectant or breastfeeding mothers because of feared side-effects for the mother and child [29]. While data are available indicating that also the expectant mothers themselves would prefer psychotherapy to pharmacotherapy or other types of intervention for mental problems as well [31], limited evidence is available for the efficacy of psychotherapy during pregnancy due to a low number of studies and small sample sizes [e.g. 32, 33]. Pregnant and breastfeeding mothers are indeed routinely excluded from biomedical research. As F. Baylis [34] pointed out: "*this is unethical and unscientific and regulators must mandate change*". Indeed, our knowledge on health-related psychobiological processes in this life period is limited, and so is our related ability to effectively treat and prevent mental disorders, including sleep problems. This limitation needs to be overcome as guidelines demand that efficacious psychological treatments should be available to pregnant women [33].

European and American guidelines [9, 35] underline that insomnia is effectively treated by cognitive behavioral therapy for insomnia (CBT-I), which is the first-line treatment for insomnia and related problems. Cumulative evidence shows that CBT-I has a beneficial effect on comorbid symptoms [36, 37], thus having the potential to prevent negative health outcomes [38].

Targeting sleep during pregnancy offers huge potential gains both from a research and a clinical perspective, to alleviate women's night and daytime sleep-related symptoms as well as for preventive

effects. As stated above, sleep is a crucial risk factor for depression and mental disorders during pregnancy. CBT-I is effective for comorbid symptoms [1-4], easily implemented in standard care and, thus, could, represent an efficacious preventive intervention [9].

In addition, a study was conducted to investigate the preferences of 187 pregnant women regarding the treatment of insomnia. Results showed that most participants (51%) preferred CBT-I as a treatment for insomnia over pharmacotherapy (12%) or acupuncture (37%). Participants also perceived CBT-I to be the most credible treatment and expected it to be the most effective for them personally [39].

Summarizing the state of the art on evidence-based literature evaluating the efficacy of health and clinical interventions for sleep problems during pregnancy, sleep complaints are prevalent and have important health consequences. Nevertheless, as stated above, these problems are often under-recognized and undertreated in clinical settings. It is so far not clear which treatments are proposed to be effective and which have received empirical support and should be implemented across pregnancy primary care. Systematic reviews and meta-analyses are useful to identify the state of the art on a specific topic and to underline whether there is a lack of evidence requiring more attention from the scientific community. Thus, there is urgency to systematically review the evidence-based literature on this specific topic and to evaluate its consistency and quality to direct future clinical and research advances in this area of healthcare. The present work aimed to systematically identify and critically assess the evidence for the use of different interventions (pharmacological, psychological, behavioral, and alternative interventions) in order to ameliorate sleep quality, sleep complaints and insomnia during pregnancy.

Methods

The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) recommendations for reporting systematic reviews and meta-analyses [40] (see Document S1 in Supplemental Material) and preregistered in the PROSPERO database, registration ID: CRD42019117295.

Study selection

Study eligibility was assessed using the Population, Intervention, Comparison, Outcomes and Study design (PICOS) approach [41]. PICOS is a structured approach for framing questions using five components: the patient population or the disease being addressed (P), the interventions or exposure (I), the comparison group (C), the outcome or endpoint (O), and the study design chosen (S). In order to be included, studies had to fulfill each of the following inclusion criteria: 1) Population: pregnant women of any age and any gestational age; 2) Intervention: clinical intervention targeting sleep quality, sleep complaints, insomnia or insomnia-related symptoms; 3) Comparison group and Outcomes: pre- and post-treatment data for both intervention and controls (when available) for one or more sleep-related outcomes, including the primary outcomes of insomnia symptoms, sleep quality and the secondary outcomes of sleep parameters (total sleep time, sleep onset latency, wake after sleep onset, sleep efficiency index), fatigue, somnolence and mood; 4) Study design: clinical studies reporting results as either pre-post means and standard deviations or standard errors (SD/SE) in all groups, change-scores in all groups, or effect sizes (e.g., Cohen's d, Eta^2); 5) Language: English, Italian, German, Spanish, French. No publication period restriction was made.

Search procedure

Several strategies were used to identify the final study sample.

No time restriction was applied in order to collect data from all studies published so far on the topic. First, databases "Pubmed", "PsycINFO" and "Medline" were systematically searched without starting

time restriction until 3rd May 2019 according to the following expression: (((pregnan*[Title/Abstract] OR "expect* mother*"[Title/Abstract] OR "mother*"[Title/Abstract])) AND ((insomnia*[Title/Abstract] OR sleep*[Title/Abstract])) AND ((treat* [Title/Abstract] OR therap*[Title/Abstract] OR intervention [Title/Abstract]))). First and third authors conducted the literature search, screened titles and abstracts of potentially eligible studies, examined the full texts and extracted descriptive data collaborating whenever the inclusion or exclusion of one study was doubtful. The final selection of articles was discussed by the first and last authors.

Second, we expanded our search through identifying further studies from the references of the screened full-texts.

Third, in order to collect data from non-published studies, the first author screened published conference proceedings from sleep-related journals from 2014 to 2019. Moreover, we contacted authors in the field (mailing list of the *European Insomnia Network*) to obtain further data and, if needed, to obtain additional information, especially on potential overlaps between samples of different studies. The searches and the screening was run on Citavi 6 software (https://www.citavi.com).

Data extraction:

The first and the third authors independently extracted data to confirm accuracy. Any doubt was discussed together with the help of the other authors. For each selected study, socio-demographic, clinical and methodological variables were extracted. When provided, data on maternal age (in years), gestational age (in weeks), trimester, parity were also extracted. Specifically, we extracted the following data: information about population characteristic (clinical/non clinical); sample size; mean age; mean age per group; age range; mean gestational age; mean gestational age per group; parity; study design; country; intervention; control; duration of the intervention; number of sessions; duration

of each session (or medication dose); intervention's conductors; sleep outcome; other outcome; follow ups.

Risk of bias assessment:

Since non- randomized controlled trials (RCT) used very different study designs often associated with high risk of bias, we conducted a systematic risk of bias assessment only for the RCT studies. Particularly, we used the Cochrane Collaboration's tool for assessing risk of bias [42]. This tool assesses the following potential areas of bias:

1) Selection bias: evaluation of recruitment and randomization methods;

2) Performance bias: evaluation of the blinding of participants and personnel.

3) Detection bias: evaluation of awareness of outcome assessors about the intervention or exposure status of participants;

4) Attrition bias: evaluation of withdrawals and drop-outs;

5) Other sources of bias: a) Confounders: evaluation of important differences between groups prior to the intervention on confounding variables (e.g., race, sex, marital status, age, health status); b) Data collection methods: evaluation of validity and reliability of instruments.

Bias is assessed as a judgment (high, low or unclear) for individual elements of these five domains. The first and the second authors independently rated each study, and disagreements were resolved through decision by consensus. For judging each item of each domain first and second authors used the grid created by Cochran Collaboration [42] in which specific criteria are explained. The final score identified whether a study was either at low, unclear or high risk of bias, following the Cochrane Collaboration guidelines.

Results

Study selection

Figure 1 illustrates the detailed flow chart of the selection process. Database searching yielded 3225 abstracts (PubMed: n = 1748; PsycINFO: n 439; Medline: n= 1038). Of these, 1420 were duplicates; after removing duplicates a total of 1805 abstracts remained. Titles and abstracts were examined for relevance and 1785 were excluded. Reference lists of the retrieved original articles were screened but no more records were found. Twenty records were scrutinized and 4 studies were excluded for the following reasons: study design (no intervention studies; n=2); outcome assessed (no sleep related outcome; n=2). A total of 16 studies met the inclusion criteria and were therefore reviewed.

Please insert here **Fig**. 1: Search flow diagram

Study characteristics

A summary of the included studies is reported in Table 1. Additional qualitative information is reported in supplementary material in Document S2. Of the included studies, six were RCT [43-48], testing the efficacy of the following different interventions: use of lavender cream, pharmacotherapy, CBT-I, relaxation exercise, use of lactuca seeds and sleep hygiene. Ten were non-randomized trials testing the efficacy of acupuncture [49]; mindful yoga [50]; music listening relaxation [51] and general relaxation [52, 53]; cognitive behavioral therapy interventions [54, 55]; mindfulness [56]; massage therapy [57] and tai-chi [58]. The sample size of all included studies ranged from a minimum of 13 to a maximum of 215 participants. The studies included data from 1252 women, aged on average 28.9 years. Reported mean gestational age varied across studies from 17 weeks to 30 weeks with five studies not reporting

this information [43, 46, 51, 53, 58]. Only three studies [47, 50, 53] had a sample composed of nulliparous women exclusively. Studies were conducted in 12 different countries, the 50% in the United States and none in Europe. Of the included studies, six included healthy women with no complaints [46, 50, 52, 53, 55, 57], seven included healthy women with self-reported sleep problems [43, 44, 47-49, 51, 54]; one study had participants with insomnia diagnosis [45], one reported data for obese women [56] and one included women with clinical depression [58]. Furthermore, the majority of the included studies (n=10) used only self-reported measures as outcomes; two studies [44, 53] used only actigraphy and four studies [45, 50, 54, 55] used both subjective/objective sleep parameters (diaries or actigraphy) and self-reported measures. Only four of the included studies carried out follow ups [43, 44, 48, 53].

Please insert here: **Table** 1: "Study characteristics"

Risk of bias assessment for randomized controlled trials

Detailed risk of bias assessment evaluations are presented in supplementary material Document S3 including judgments (low risk, unclear or high risk) and reasons based on Cochrane's criteria.

Risk of bias assessment scores are presented in Figure 2. Only one study [45] had a judgment of "high risk" in the attrition bias. Indeed, in this study, despite attrition and exclusions were reported, the attrition rates differed between the two groups (intervention/control). One study [46] had four "unclear" judgments as there was a lack of detailed information regarding allocation concealment, blinding of participants, and no study protocol was reported.

Please insert here **Fig.** 2: "Quality of randomized controlled trials"

Critical evaluation of level of evidence of non-randomized controlled trials

Ten studies were non-RCT (n=10). Of these, two studies had no control group [52, 54], and one further study used baseline data of women who began the intervention in the third trimester of pregnancy as the control for post-treatment [50]. Three studies did not report mean gestational age [51, 53, 58] of the participants, and only one study [53] included follow-up analyses. Finally, the majority of the non-RCT studies had exiguous samples, indeed seven studies had a sample with less than 40 participants [49, 50, 52-55, 57].

Efficacy of cognitive behavioral interventions

As stated before, CBT-I is a non-pharmacological insomnia-focused psychotherapy, recommended as

the first-line treatment for insomnia by American and European guidelines [9, 35]. CBT-I has also been identified by pregnant women as their treatment of choice, compared with pharmacotherapy and acupuncture [39]. However, little is known about its effectiveness for prenatal insomnia. In our systematic review four studies tested the efficacy of CBT-I or cognitive behavioral therapy (CBT) strategies on sleep and insomnia-related outcomes.

Manber et al. [45] evaluated through a RCT the efficacy of CBT-I compared to psychoeducation control therapy in an ethnically diverse sample of pregnant women who were not depressed and did not receive any other treatments for insomnia disorder. The primary outcome was the insomnia severity score [59] and secondary outcomes were rates of remission of insomnia disorder, objective and self-report measures of time awake at night (i.e. total wake time), and depression symptoms. Results showed that women who received CBT-I had greater improvement in insomnia symptom severity; shorter time to remission time of insomnia; reduced self-reported total wake time and reduced depression symptoms compared to control therapy.

Tomfohr-Madsen et al. [54] assessed the efficacy of 5-weeks CBT-I intervention in a pilot study on 13 healthy pregnant women (mean gestational age 19.31 weeks) with self-reported sleep problems. Outcomes of this study were insomnia symptoms and sleep parameter measured with both sleep diaries and actigraphy. Results showed that on average insomnia symptoms decreased such that participants no longer reported clinically significant insomnia after treatment. Sleep diary variables including total sleep time and sleep efficiency significantly increased after the intervention. Actigraphy results showed a significant increase of sleep efficiency and decrease of sleep onset latency after the intervention.

Lee et al. [55] tested the efficacy of a sleep health behavioral education intervention compared to usual prenatal care on 25 healthy pregnant women (on average at 29th gestational week). Results showed that the intervention significantly reduced self-reported insomnia symptoms compared to the control group.

No other significant results in other outcomes were found.

Finally, Rezaei et al. [48] conducted a RCT in 112 healthy pregnant women with self-reported sleep problems in order to test the efficacy of sleep health behavioral education compared to usual prenatal care. Results showed that sleep quality was increased after intervention and at follow up compared to before intervention.

Efficacy of pharmacotherapy intervention

Pharmacotherapy for insomnia is frequently prescribed off-label, for example benzodiazepine receptor agonists, antidepressants, and gamma-aminobutyric acid reuptake inhibitors [60]. Regarding the possible side effects of pharmacotherapy for treatment of insomnia in prenatal period, some authors suggested that benzodiazepine and benzodiazepine receptor agonists are associated with increased risk of preterm labor, low birth weight and small-for-gestational-age infants [61]. Particularly, zolpidem has been associated with preterm birth, cesarean birth, and low-birth-weight infants [62].

Khazaie et al. [44] performed a RCT in order to investigate the efficacy of pharmacotherapy (trazodone and diphenhydramine) compared to placebo on objectively measured sleep parameters. They found no significant differences after 2 weeks of treatment between the two groups. However, after 6 weeks of treatment the experimental group showed longer sleep duration and higher sleep efficiency compared to placebo group. Participants in both trazodone and diphenhydramine groups reported daytime sleepiness as most frequent side-effect.

Efficacy of mindfulness and yoga interventions

Mindfulness derives from the tradition of meditation where individuals exercise an intentional awareness to present thoughts and sensations with acceptance and no judgment [63, 64]. Mindfulness strategies play a role in reducing stress and regulating emotional reactivity. Both mechanisms are

particularly useful in attenuating the cognitive and somatic arousal associated with insomnia [65]. Increasing evidence suggests that mindfulness-based interventions may improve well-being during pregnancy. Furthermore, yoga intervention studies reported that yoga significantly improves sleep quality, for example, results from one study suggest that yoga may be efficacious to sleep [66]. They implemented a prenatal yoga intervention and demonstrated significantly lower incidences of adverse perinatal outcomes in the treatment group compared to controls.

In our systematic review, one study from Beddoe et al. [50] assessed the efficacy of a 7 week mindfulness based yoga intervention on subjective and objective sleep quality and sleep pattern in pregnant women. They found that women who began the yoga program in their second trimester reported less wake time and less perceived sleep disturbance versus women who began the intervention in their third trimester. The study from Felder et al. [56] assessed the efficacy of a Mindfulness Mom Training (MMT) compared to treatment as usual (TAU) on sleep quality in 215 obese/overweight pregnant women. MMT included elements to support healthier eating and encourage physical activity, and focused on increasing attention to awareness of physical sensations, thoughts, and emotions, and accepting negative experiences versus ruminating about them. They found that MMT participants did not experience significantly greater improvement in sleep quality compared to TAU participants. However, poor global sleep quality predicted increased depression symptoms for both groups.

The last study included in our systematic review that assessed the efficacy of yoga and tai-chi intervention compared to waiting list control on subjective sleep quality in 92 women with clinical depression was by Field et al. [58]. They found that the tai chi/yoga group showed greater decreases in self-reported sleep problems as well as in depression and anxiety scores compared to the control group.

Efficacy of relaxation interventions:

Several studies on relaxation exercises during pregnancy indicate that these exercises have various

effects on biological and psychological stress systems, prolong pregnancy in pregnant women with preterm delivery risk, and increase birth weight [67-69].

In our systematic review, five studies assess the efficacy of relaxation intervention on sleep quality in pregnant women.

The first study from Liu et al., [51] evaluated the effects of a two-week relaxation intervention, consisting in listening to music, compared to usual prenatal care, in healthy Taiwanese pregnant women with self-reported sleep quality problems. Pregnant women in the experimental group were instructed to listen to at least one disc (30 minutes) or a minimum of 30 minutes of their preferred music per day at bedtime for two weeks. Women in the experimental group reported significantly higher sleep quality after this time.

Moreover, Schaffer et al. [52] tested the efficacy of an 8-week guided imagery relaxation intervention on self-reported sleep quality in 20 healthy pregnant women. The intervention used a professionally produced CD (compact disc). Each track provided images to promote increased relaxation, capacity to work with difficult feelings, and self-empathy. Study participants were asked to listen to a track at least once a day but could listen more than once. They were advised to use the CD at any time of the day they preferred. They found that as the average amount of time spent listening per week increased, Pittsburgh Sleep Quality Index (PSQI) [70] scores decreased.

The third study included [57] focused on massage and relaxation interventions. Authors found that massage and relaxation interventions twice a week for five weeks had a positive impact on pregnant women by decreasing stress hormones and potential stressors, and improving mood and sleep.

Furthermore, Ozkan et al. [46] assessed the efficacy of a relaxation intervention with a RCT. Particularly, pregnant women were provided with a CD with relaxation exercises to perform at bed

time for 4 weeks. Their sleep quality was assessed by PSQI at baseline and at post-intervention. The study found significant differences between the relaxation exercises group and the control group in terms of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, and daytime dysfunction in favor of the relaxation exercises group.

Finally, Lee et al. [53] evaluated the effect of Sleep Enhancement Training System for Pregnancy treatment in a sample of 25 healthy pregnant women aged on average 32.7 years. Sleep Enhancement Training System for Pregnancy was a 4-weeks intervention during which women were instructed to listen to material provided on an MP3 player before going to sleep each night. The sound-enhanced relaxation training included guided imagery, muscle relaxation, and breathing techniques to reduce arousal and promote sleep. Participants in the control group were provided with a pamphlet containing recommendations for healthy eating and information about how diet can influence sleep. Two sleep-related outcomes were evaluated using actigraphy: nocturnal sleep duration (total sleep time in minutes) and nocturnal sleep disruption (wake after sleep onset in minutes). Results showed that participants in the experimental group had significantly longer sleep duration and less sleep disruption compared to participants in the control group, and also that this effect was stronger at the follow-up assessment (one month after delivery).

Efficacy of alternative interventions

Several alternative treatments for insomnia have been suggested, including for example acupuncture, acupressure, aromatherapy, foot reflexology, homeopathy, meditative movement therapies, moxibustion [35]. Despite that, studies underlying this evidence are methodologically poor and thus the generalizability of results is difficult to evaluate.

In our systematic review, Guerreiro da Silva et al. [49] evaluated the effect of acupuncture. This

intervention study evaluated the effect of acupuncture and sleep hygiene compared to only sleep hygiene on self-reported sleep problems in 30 pregnant women. They found that both groups reported less insomnia symptoms after the intervention, but that the reduction was greater in the group involved in acupuncture and sleep hygiene intervention. Moreover, they did not find important adverse effects of acupuncture effects during the study and in the post-partum period.

Furthermore, two studies were included that evaluated the effects of herbal medication treatment.

Effati-Daryani et al. [43] evaluated the effect of lavender cream with or without footbath, compared to placebo, on sleep quality and fatigue in pregnancy and postpartum with an RCT. The sample of this study was composed of 141 pregnant women aged 18 to 40 years, whose parity was one to three and who were at 25 to 28 weeks of gestation and with self-reported sleep problems. They found that the Lavender and footbath group showed an increase in sleep quality both during pregnancy and at follow up (6 weeks after the delivery), and decreased fatigue scores only at follow up assessment.

Finally, Pour et al. [47] performed an RCT on the effect of Lactuca sativa L. seeds on 100 outpatient pregnant women who complained of insomnia. Women aged 20 to 45 years with singleton pregnancies and at a gestational age of 12 to 36 weeks were included. Participants in the experimental group were asked to take one capsule every night for two weeks (lettuce seed group), while the control group received placebo capsules. Results showed that intervention was efficacious in improving sleep quality in the experimental group.

Synthesis and conclusion

This is the first systematic review assessing current evidence of interventions for sleep problems and complaints during pregnancy. We included sixteen studies involving different types of interventions and study designs. For this reason, results are not statistically comparable in terms of outcome, type of design and type of intervention. Despite that, in table 2 we summarized the main results for each study, highlighting intervention type, characteristic and assessed outcome.

Please insert here **Table** 2: Efficacy of different intervention on assessed outcome

CBT-I interventions appear to be efficacious in pregnant women. Tomfohr-Madsen et al. [54] provided promising results showing that CBT-I is well-received and promote an amelioration of sleep in pregnant women. However, this non-RCT study was based on data of only 13 pregnant women. The study from Manber et al. [45] assessed the efficacy of CBT-I using a larger sample size and a RCT design, and it seems to confirm the results from Tomfohr-Madsen et al. [54]. Lee et al. [55] implemented a sleep health behavioral intervention of only seven days and did not find significant improvement in sleep quality and sleep parameters assessed through questionnaires and diaries, but only in self-reported sleep disturbance, suggesting that longer interventions are desirable. In summary, CBT-I and CBT strategies appear to be effective in improving sleep outcomes in pregnant women, confirming what is already known in the general population [9, 35]. Despite that, our systematic review highlighted a substantial lack of evidence.

Based on the study conducted by Khazaie et al. [44], pharmacotherapy seems to be associated with long-term improvements, but no post-treatment effect. Despite that, the authors reported that the majority of women involved in the study complained about daytime sleepiness as principal side effect.

It seems reasonable that, similarly to the general population, CBT-I is to be preferred for symptoms of insomnia in pregnant women, also because pharmacotherapy daytime side-effects could be associated with negative pregnancy outcomes or increased maternal stress in this population.

Regarding mindfulness and yoga interventions, the only study that did not find significant improvement after the intervention is the one by Felder et al. [63]. This could be due to the fact that the sample of this study was composed of obese/overweight pregnant women, and it is known in literature that there is an association between obesity and increased sleep disturbance [71-73].

Relaxation interventions seem to be efficacious in improving sleep and insomnia-related outcomes. Despite that, only one study [53] assessed the efficacy of this type of intervention in our systematic review and performed one follow-up assessment at 1 month after the delivery. Based on this study, the effect of this intervention was efficacious both at post-treatment and at follow up assessment.

Studies on alternative medicine report positive effects on sleep outcomes. However, they used self-reported measures, including only questionnaires, and they did not use more ecological measures as sleep diaries or objective or physiological measures. For this reason, in order to assess the efficacy of this type of intervention, more studies using long-term, ecological self-report and physiological measures (like for instance sleep ~~diaries, actigraphy~~diaries, actigraphy and/or polysomnography ~~polisomonography~~ and other physiological measures) are needed.

This first systematic review on this topic outlines a severe lack of evidence for clinical preventive and curative support for sleep problems in pregnant women. Despite the large number of women complaining of sleep problems during pregnancy, there is a lack of evidence-based interventions, thus limiting clinical judgment on efficacious treatments. Systematic reviews can demonstrate where knowledge is lacking and, consequently, guide future research to overcome the neglecting of the topic in research and clinical context [74].

More effort should be dedicated to clinical research assessing the effectiveness of diverse interventions for sleep problems in this important period of life for both women and for their children. There is a need to improve psychological health care during pregnancy to support a positive course of pregnancy, birth and post-partum. Future clinical studies should be rigorously RCTs, and should conduct follow-ups after the interventions in late pregnancy, and post-partum. Thus, long-term efficacy of the interventions should be evaluated. ~~Studies~~ Researchers should recruit large samples of women in order to improve statistical power and and to clearly distinguish the nature of sleep problems in pregnancy, particularly between sleep problems and insomnia. Furthermore, since it is well known that physical activity and exercise have a lot of positive health outcome (including ameliorating sleep quality), future clinical studies and RCTs should assess the efficacy of these type of intervention for sleep problems in this population. An important objective would be to repeat this work in the next years and have the possibility to conduct meta-analytic computations, such as a network meta-analysis. This is a statistical method that allows to evaluate the effectiveness of multiple treatments simultaneously combing direct and indirect evidences of treatment differences and to promote guidelines for best-supported evidence-based interventions for insomnia during pregnancy. Indeed, a limitation of this systematic review is that the magnitude of the effects of specific types of interventions was not considered with a meta-analysis. Consistently, studies included in this systematic review assessed the efficacy of very different interventions that were dissimilar from each other in some crucial variables (outcome assessed, type of design and type of intervention). For this reason, and following Cochrane Collaboration [41] and Prisma Guidelines [42] a comprehensive measure of all the effects with meta-analytic calculation would not be informative. Finally, another limitation is due to the low number of studies also using different interventions. Therefore, it is still early to provide clinical guidelines. This limits the possibility of commenting and critically evaluating the literature currently available.

Following the current guidelines, we recommend to test the efficacy of cognitive-behavioural treatment

for insomnia in large RCT and test its efficacy for sleep and comorbid outcomes in a long-term perspective.

Practice points:

1. Sleep disorders are among the most widespread major problems experienced during pregnancy. The National Sleep Foundation's Women and Sleep Survey in 2007 found that up to 78% of pregnant women report disturbed sleep.

2. Despite the high prevalence and their association with many negative outcomes, insomnia and sleep complaints during pregnancy are underdiagnosed and undertreated.

3. There is a lack of guidelines regarding evidence-based interventions for insomnia which work and should be offered to pregnant women.

Research agenda

1. There is a need to improve psychological and sleep health care during pregnancy to support a positive course of pregnancy, birth and post-partum. Future clinical studies should be rigorously randomized controlled trials, follow-up women after interventions in late pregnancy and post-partum. Thus, long-term efficacy of the interventions should be evaluated. Studies should recruit a large number of women in order to improve statistical power.

2. Following the current guidelines for insomnia, we recommend to test the efficacy of cognitive-behavioral treatment for insomnia in large randomized controlled trials and test its efficacy for sleep and comorbid outcomes in a long-term perspective.

Acknowledgements

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Table 1: Study characteristics

Study	Population characteristics	Sample size	Mean age (years)	Mean Gestational Age (weeks)	Study design	Country	Interventions	Duration of the intervention	Sleep outcome
Beddoe AE et al., 2010 [50]	Healthy	15	30.2	23.3	Intervention study	USA	Mindfulness based yoga vs baseline data	7 wk	Self-reported sleep disturbance and sleep parameter by actigraph
Effati-Daryani F et al., 2018 [43]	Healthy, with reported sleep problems	141	27.7	27.7	Randomized controlled trial	Iran	Lavender cream with or without footbath vs placebo	During pregnancy and two wk after the delivery	Self-reported sleep quality and fatigue
Felder JN et al., 2018 [56]	Obese / Overweight women	215	27.8	17.4	Intervention study	USA	Mindful moms training (MMT) vs treatment as usual	8 wk	Self-reported sleep quality
Field T et al., 1999 [57]	Healthy	26	29	23.5	Intervention study	USA	Massage therapy vs control relaxation therapy	5 wk	Self-reported sleep disturbance
Field T et al., 2013 [58]	Women with clinical depression	92	26.6	22	Intervention study	USA	Yoga & tai chi vs waiting list	12 wk	Self-reported sleep disturbance
Guerreiro da Silva JB et al., 2005 [49]	Healthy, with reported sleep problems	30	26.5	21.4	Prospective, quasi-randomized, controlled study	Brazil	Acupuncture vs sleep hygiene	8 wk	Self-reported sleep disturbance

Lee KA et al., 2016 [53]	Healthy	25	32.7	29	Intervention study	USA	Home-based sleep enhancement training system for pregnancy vs control groups of another study	4 wk	Sleep parameter by actigraph
Lee KA & Gay CL, 2017 [55]	Healthy	25	32.9	29	Non-Randomized Controlled Pilot Study	USA	Sleep improvement protocol from antepartum patients (SIP-AP) vs usual prenatal care	7 d	Self-reported sleep disturbance, sleep quality and sleep duration, sleep parameter by sleep diaries
Liu YH et al., 2016 [51]	Healthy, with reported sleep problems	121	Not reported	Not reported	Not randomized controlled trial	Taiwan	Music therapy (Listening CD) vs usual prenatal care	2 wk	Self-reported sleep quality
Khazaie H et al., 2013 [44]	Healthy, with reported sleep problems	54	26.5	28	Randomized controlled trial	Iran	Trazodone;Diphe nhydramine vs Placebo	6 wk	Sleep parameter by actigraph
Manber R et al., 2019 [45]	Insomniac	179	33	24.7	Randomized controlled trial	USA	Cognitive behavioral therapy for insomnia (CBT-I) vs control therapy	5 wk	Self reported severity of insomnia; sleep parameter by sleep diaries and actigraph
Özkan SA & Rathfisch G, 2018 [46]	Healthy	84	27.8	Not reported	Randomized controlled trial	Turkey	Relaxation vs standard care	4 wk	Self-reported sleep quality, sleep duration and sleep disturbances

Pour ZS et al., 2018 [47]	Healthy, with reported sleep problems	100	29.4	30.6	Randomized controlled trial	Iran	Lactuca sativa L. seeds vs placebo	2 wk	Self reported sleep quality
Rezaei E et al., 2014 [48]	Healthy, with reported sleep problems	112	26.8	17.8	Randomized controlled trial	Iran	Education of sleep health behavior vs usual prenatal care	4 wk	Self reported sleep quality
Schaffer L et al., 2013 [52]	Healthy	20	27.3	28	Intervention study	USA	Relaxation guided imagery	8 wk	Self reported sleep quality
Tomfohr-Madsen LM et al., 2017 [54]	Healthy, with reported sleep problems	13	31	19.3	Intervention study	Canada	Cognitive behavioral therapy for insomnia (CBT-I)	5 wk	Self reported severity of insomnia; sleep parameter by sleep diaries and actigraph

Table 2: Efficacy of different intervention on assessed outcome

Intervention	Randomzied Controlled Trial (Yes/No)	Number of session (n=)	Follow up (Yes/No)	Sleep quality	Self reported sleep disturbance	Sleep parameters by actigraph	Sleep parameters by sleep diaries
Cognitive Behavioral Therapy interventions							
Manber R et al., 2019 [45]	Yes	5 weeks	No		✓	✗	✓
Tomfohr-Madsen LM et al., 2017 [54]	No	5 weeks	No	✓	✓	✓	✓
Lee KA & Gay CL, 2017 [55]	No	7 days	No	✗	✓		✗
Rezaei E et al., 2014 [48]	Yes	4 weeks	Yes (1 and 2 months after the intervention)	✓			
Pharmacotherapy							

Study			Yes (2 and 6 weeks after intervention)			✓ only at follow up
Khazaie H et al., 2013 [44]	Yes	6 weeks	Yes (2 and 6 weeks after intervention)			✓ only at follow up
Mindfulness						
Beddoe AE et al., 2010 [50]	No	7 weeks	No		✓	✓
Felder JN et al., 2018 [56]	No	8 weeks	No	✗		
Field T et al., 2013 [58]	No	12 weeks	No		✓	
Relaxation						
Liu YH et al., 2016 [51]	No	2 weeks	No	✓		
Schaffer L et al., 2013 [52]	No	8 weeks	No	✓		
Field T et al., 1999 [47]	No	5 weeks	No		✓	
Özkan SA & Rathfisch G, 2018 [46]	Yes	4 weeks	No	✓	✓	

Lee KA et al., 2016 [55]	No	4 weeks	Yes (1 month after delivery)		✓

Alternative					
Guerreiro da Silva JB et al., 2005 [49]	No	8 weeks	No		✓
Effati-Daryani F et al., 2018 [43]	Yes	During pregnancy and after delivery	6 weeks after delivery	✓	
Pour ZS et al., 2018 [47]	Yes	2 weeks	No	✓	

(Legend: ✓ = the intervention was efficacy in this outcome; ✗ = the intervention was not efficacy in this outcome)

PRISMA 2009 Flow Diagram

Identification

Records identified through
database searching
(n = 1748 Pubmed
n= 1038 Medline
n= 439 Psychinfo)

Additional records identified through other
sources (contact with experts, search for
abstracts in conference proceedings;)
(n =0 abstracts in conference proceedings

Screening

Duplicates removed
(n = 1420)

Records (abstracts) screened
(n =1805)

Records (abstracts) excluded
(n =1785)
Reasons:

Population: pregnant women
Study design: clinical intervention targeting
sleep quality, insomnia or insomnia related
symptoms
Comparator group and Outcomes: pre and
post treatment data for both intervention
and controls (when available)

Eligibility

Full-text articles assessed
for eligibility
(n = 20)

References' screening of the
screened full-texts.
(n = 0)

Full-text articles excluded, with
reasons

n = 2 (Study design)
n = 2 (Not insomnia or sleep as
primary or secondary outcome)

Studies included in qualitative synthesis
(n = 16)