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Polysomnographic features of pregnancy: a systematic review

Short title: Polysomnography in pregnancy

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SUMMARY

Symptoms of sleep disturbances are common among pregnant women and generally worsen across gestation. Pregnancy-related sleep disorders are not only associated with a poor quality of life of the affected mothers, but also with adverse perinatal outcomes, including perinatal depression, gestational diabetes, preeclampsia, and preterm birth. The current knowledge about the impact of sleep disorders during pregnancy largely derives from the results of sleep surveys conducted in various populations. However, the number of studies examining changes in objective sleep variables during pregnancy via polysomnography has progressively increased in recent years.

Here we systematically reviewed the polysomnographic studies available in the literature with the aim to describe the sleep pattern and to identify possible markers of sleep disruption in pregnant women.

Based on our analysis, subjective worsening of sleep quality across gestation is related to objective changes in sleep macrostructure, which become particularly evident in the third trimester. Pregnancy per se does not represent an independent risk factor for developing major polysomnography-assessed sleep disorders in otherwise healthy women. However, in women presenting predisposing factors, such as obesity or hypertension, physiological changes occurring during pregnancy may contribute to the onset of pathological conditions, especially sleep-disordered breathing, which must be carefully considered.

Keywords

Pregnancy, polysomnography, sleep stages, OSA, sleep-disordered breathing, adverse fetal outcomes, hypertensive disease of pregnancy, gestational diabetes mellitus

Abbreviations

AHI: Apnea-hypopnea index	PE: Preeclampsia
BMI: Body mass index	PLMS: Periodic leg movements during sleep
CHTB: Chronic hypertension	PLMSI: Periodic leg movements during sleep index
CPAP: Continuous positive airway pressure	PSG: Polysomnography
EEG: Electroencephalography	PSQI: Pittsburgh sleep quality index
EMG: Electromyogram	RDI: Respiratory disturbance index
EOG: Electrooculogram	REM: Rapid eye movement sleep
ESS: Epworth sleepiness scale	RLS: Restless legs syndrome
GA: Gestational age	SaO2: Oxygen saturation
GCT: Glucose challenge test	SDB: Sleep-disordered breathing
GDM: Gestational diabetes mellitus	SE: Sleep efficiency
GHTN: Gestational hypertension	SOL: Sleep-onset latency
HDP: Hypertensive disease of pregnancy	SWS: Slow wave sleep
NREM: Non-rapid eye movement sleep	TCO2: Transcutaneous CO2
ODI: Oxygen desaturation index	TIB: Time spent in bed
OGTT: Oral glucose tolerance test	TST: Total sleep time
OSA: Obstructive sleep apnea	WASO: Wake after sleep onset
PaO2: Partial pressure of oxygen	

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1. Introduction

Pregnancy is a physiological condition of relatively short duration in a woman's life, but characterized by profound biological changes, which have a significant influence on sleep [1].

The typically increased secretion of several hormones across pregnancy considerably impacts on both the circadian and homeostatic components of sleep regulation, leading to modifications of sleep architecture [2]. In human studies, non-rapid eye movement sleep (NREM) has been shown to be enhanced by progesterone and prolactin [3,4], while rapid eye movement sleep (REM) is decreased by progesterone and increased by estrogens [5,6]. Oxytocin peaks during the night, promoting uterine contractions leading to sleep fragmentation [2]. Cortisol and growth hormone levels are also elevated, affecting sleep quality and inducing daytime sleepiness [2].

Besides hormones, other factors contribute to sleep disruption during pregnancy: gastroesophageal reflux, affecting up to 75% of pregnant women [7]; nocturnal micturition, due to an increase in overnight sodium excretion [8]; anatomical changes related to the growing uterus and increased body weight [9]. Moreover, iron and folate deficiency may play a role in the occurrence of sleep-related movement disorders in pregnant women [10,11].

Subjectively reported sleep disturbances are very common during pregnancy, with increasing rates from the first (13%), to the second (19%), and third (66%) trimester of gestation [12,13]. A recent meta-analysis showed that 46% of women experience poor sleep quality during pregnancy, with an average score of the Pittsburgh Sleep Quality Index (PSQI) of 6.4 (95% CI, 5.3-6.85) and with a worsening trend from the 2nd to the 3rd trimester by an average of 1.68 points (95% CI, 0.42-2.94) [14]. While at early gestational age women mainly attribute sleep problems to nausea/vomiting, urinary frequency, and backpain [15], in late gestation up to 69.9% of women report difficulty in maintaining sleep, 34.8% early morning awakenings, and 23.7% difficulty falling asleep [16], mainly due to fetal movements, heartburn, cramps or tingling in the legs, and shortness of breath

[13,17–19]. By the end of pregnancy almost all women suffer from recurrent and long wake episodes during the night [17,20].

Self-reported sleep duration also declines across pregnancy [21]. Moreover, objectively assessed sleep duration and quality are related to age and ethnicity, with non-Hispanic black and Asian women having the shortest sleep duration, and younger pregnant women having the highest amount of wake after sleep onset (WASO), the lowest sleep efficiency (SE), and the latest sleep midpoint [22].

To date, the available literature on sleep during pregnancy is mostly based on subjective information from screening questionnaires or interviews [14,19]. However, in recent years, an increasing number of studies investigated sleep in pregnant women objectively, by using polysomnography (PSG) or actigraphy. Sleep parameters derived from actigraphy may significantly differ from those obtained by PSG recordings and should be therefore interpreted with caution [23]. Thus, PSG remains the gold standard for sleep depiction, being the only reliable tool to precisely describe sleep macro- and microstructure, correctly estimate respiratory and motor events, and permit an accurate identification of pregnancy-related sleep disorders.

We here present the first systematic review of polysomnographic studies conducted in pregnant women, with the aim to provide a detailed overview about the intrinsic, objective features of sleep in normal, healthy pregnancy, as well as in some typical pregnancy-related complications.

2. Methods

We performed a systematic review of the literature by searching for studies reporting objective sleep parameters obtained by polysomnography (PSG) in pregnant women until February 1, 2019.

The review process followed the PRISMA statement guidelines [24]. The completed PRISMA checklist can be found in the supplementary material section (table S1).

2.1. Search strategy

The terms 'pregnancy' OR 'gestation' AND 'polysomnography' OR 'PSG' were searched in the databases Medline, Scopus and Embase. The search terms had to be included in the Title, Abstract or Keyword section of the articles. The first author reviewed the automatically generated list of items and classified every manuscript, based on its abstract, as "eligible", "not eligible" and "maybe eligible", according to the selection criteria described below. Articles considered "not eligible" were excluded from a further analysis. Afterward, the first and second authors independently examined the "eligible" and "maybe eligible" full-text articles in a blinded fashion, to determine whether they met the criteria to be included in the review. The inter-rater agreement calculated as Cohen's kappa coefficient (κ) was 0.92. In case of disagreement, they consulted the senior author (MM) for a final decision.

2.2. Selection criteria

The following criteria were applied:

1) Sleep assessment: only studies reporting PSG data recorded during pregnancy and using a minimal montage of at least one EEG channel either in mono- or bipolar, electrooculogram (EOG), chin electromyogram (EMG) were included. Studies based on other objective sleep assessment methods than PSG (e.g. actigraphy or polygraphy) or using subjective tools (e.g. questionnaires) were excluded;
2) Number of nights recorded: at least one full night PSG recording
3) Sample size: only studies with a sample size of $\geq$ 10 women
4) Language: English;

5) Type of study: original studies on human subjects; no single case reports, reviews, commentaries/letters, editorial, conference abstracts;
6) Control group: studies including either a control group (healthy pregnant or non-pregnant women) or without a control group were included.

Additionally, the authors went through the reference lists of the selected articles to identify further studies. Unpublished manuscripts were not included.

2.3. Quality assessment

The quality assessment of the studies included in the systematic review was performed using the Newcastle-Ottawa scale (NOS) adapted for cross-sectional studies (according to Herzog et al. [25]), cohort studies, and case-control studies (available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The NOS consists of several items included in 3 domains (selection of the study groups, comparability of the groups, and outcome/exposure assessment). Each item is evaluated based on a 'star system'. Trials included in our review were evaluated using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [26] and the Cochrane Collaboration's risk of bias in non-randomized studies (ROBINS-I) [27]. The results of the quality assessment of all included studies are summarized in Table S2 (supplementary material).

2.4. Statistical analysis

Mean and standard deviation of longitudinal studies reporting TST and SE were pooled in order to evaluate changes in these sleep variables from the first to the third trimester of gestation. Weighted mean difference (WMD) with 95% confidence interval (95% CI) was used to estimate absolute differences of continuous outcomes. I^2-statistics was adopted to measure the percentage of variance attributable to study heterogeneity (I^2>50%). The Egger's weighted regression test was used to

detect publication bias. Statistical analysis was performed using StatsDirect software version 3.0 (Cambridge, UK).

3. Results

3.1. Literature search

A detailed flowchart of the results of the literature search process is presented in figure 1. Finally, 40 studies were considered for the qualitative analysis (systematic review). Twenty-four of them were cross-sectional studies (n=24), ten prospective cohort studies (n=10), five clinical trials (n=5), and one case-control study (n=1). Out of 40 studies, n=27 included a control group, while n=13 were not controlled. Regarding the country of origin, most studies were performed in the USA (n=20), followed by Australia (n=9) and Canada (n=4). Sample sizes examined ranged between 10 and 234 women. A detailed overview of the main study characteristics is provided in tables S3 and S4 (supplementary material). Main findings of the reviewed studies are highlighted in table 1.

3.2. Polysomnographic findings

3.2.1. Sleep structure

Subjective perception of poor sleep quality reported by women across gestation is related to objective changes in sleep structure. We found three cross-sectional studies investigating the differences in sleep parameters of pregnant women vs. non-pregnant controls.

Hertz et al. reported a significantly decrease in SE, due to a substantial increase in WASO and number of awakenings in 12 women during late pregnancy compared to 10 age-matched non-pregnant controls [28]. Non-REM sleep (NREM) S1 was also increased in the pregnant group with, in turn, a decrease of both REM sleep and SWS. Rimpilä et al. obtained similar results studying 18 healthy pregnant in the third trimester, compared to 12 non-pregnant controls [29].

In a larger PSG investigation (27 women in the first trimester of gestation, 21 in the third trimester, and in 24 healthy non-pregnant controls), Wilson et al. [30] confirmed women during the third trimester having poorer SE, more awakenings, less stage 4 sleep, more N1 sleep and fewer minutes spent in REM sleep compared to control group. Interestingly, higher progesterone levels within third-trimester women were associated with an increase in WASO and arousals.

Three studies assessed changes in sleep parameters in the same individuals across the perinatal period in a longitudinal setting. Coble et al. [31] performed PSG at three time points during pregnancy and two during the postpartum, comparing pregnant women with (n=13, in remission) vs. without (n=20) a history of affective disorders. They found that women with a previous depression have a longer TIB and TST in early pregnancy, an earlier onset and more pronounced sleep disruption, as well as a reduced REM-latency in late pregnancy, compared to control women.
Lee et al. [32] examined women during the follicular phase (n=33), the first (n=33) and third trimester of pregnancy (n=29), as well as postpartum (n=29). Changes were already evident in the first trimester, with an increase of TST, decrease of SE and a marked reduction of SWS during pregnancy, compared to pre-pregnancy baseline. No variation in REM sleep was noted. These changes remained relatively stable in the course of pregnancy and improved after delivery.
In a secondary analysis of their 2013 dataset [33], Izci-Balserak et al. [34] evaluated changes in sleep architecture and spectral EEG bands during pregnancy in 123 women who underwent PSG in early pregnancy and in 97 of them also in late pregnancy. They found a shorter sleep duration, poorer SE, more awakenings, more stage N2 sleep, less SWS and REM sleep in late compared to early pregnancy, thus partially replicating the results from one of the first longitudinal studies on PSG-assessed sleep across pregnancy [35].

In summary, changes in sleep structure during pregnancy seem to mainly affect the third trimester of gestation, which is generally characterized by a shorter sleep duration and a more disrupted

sleep, with an increased number of awakenings and superficial sleep stages, as well as a reduction of SWS and REM sleep. These findings are more evident when comparing pregnant women with non-pregnant controls, but they have also been recently confirmed in the same individuals recorded at early and late GA [34].

3.2.2. Breathing pattern

Sleep-disordered breathing (SDB), is estimated to affect 10-32% of pregnant women, depending on its definition [36]. Obstructive sleep apnea (OSA), in particular, is estimated to be a frequent condition during pregnancy, with a pooled worldwide prevalence of 15% (95% CI 12–18%), and it has been associated with gestational hypertension, gestational diabetes, pre-eclampsia, C-section, postoperative wound complication, and pulmonary edema [37]. Moreover, OSA is related to an increased risk for preterm birth (aOR=1.62) and neonatal intensive care unit admission (aOR=1.28) [37]. Based on these findings, the analysis of respiratory parameters in pregnant women has become the main target of sleep research studies.

Guilleminaut et al. [38] screened 267 healthy pregnant women with a normal BMI (23.7±0.8kg/m^2 at study entry) regarding the presence of daytime sleepiness and snoring. A selected subgroup based on stratified questionnaire results (n=26) underwent overnight PSG. None of the subjects showed an apnea-hypopnea index (AHI)>5/h but chronic snorers presented breathing abnormalities such as esophageal pressure crescendos in N1 and N2 and abnormal sustained effort during SWS, which were associated with higher systolic and diastolic blood pressure increases, as well as a non-dipper profile in the 24h-BP recordings (six out of 13 snorers).

Small cross-sectional studies in pregnant women compared to non-pregnant controls also reported slightly decreased mean and minimum SaO2 values but no differences in AHI and/or ODI or TCO2 levels [28,29].

However, El-Helbawy et al. [39], examining 30 primiparous pregnant women vs. 30 age-matched non-pregnant controls found a higher mean AHI (4.38±4.45 vs. 1.77±1.2), ODI (3.72±4.03 vs. 2.27±1.11), and snoring index (8.19±6.87 vs. 1.08±1.75) in the pregnant group. Among pregnant women, 36.7% had a mild OSA and 53.3% were snorers. Patients with OSA had a significantly higher GA, BMI, a larger neck circumference, a higher ODI, flow limitation index, snoring index, and ESS score compared to healthy subjects. GA and BMI, in particular, emerged as independent risk factors for OSA during pregnancy, with odds ratio of 2.23 and 4.99 respectively.

Izci-Balserak et al. [34], by applying a longitudinal design, found a statistically significant increase in AHI (2.09±3.17 vs. 3.41±4.60, $p<0.002$) and OSA cases [AHI>5 events/h; n=14 (11.38%) vs. n=26 (26.80%), $p<0.004$] during late compared to early pregnancy.

An elevated BMI has been often associated with a higher risk for developing SDB during gestation. To assess pregnancy as an independent risk factor for SDB, Bourjeily et al. performed a third trimester PSG in obese pregnant women (BMI 44.1±6.9) compared to BMI- and age-matched non-pregnant controls [40,41]. AHI and oxygen desaturation showed no differences between groups, with 8/25 within the case group qualifying as OSA (AHI≥5/h). However, pregnant women had significantly more flow limitations during TST and in each sleep stage compared to controls.

Maasilta et al. [42], compared obese with normal weight women, during early and late pregnancy. They found no difference in sleep structure, but an increase in AHI (1.7/h vs. 0.2/h; $p<0.05$), RDI (7.4/h vs. 0.8/h; $p<0.001$), ODI (5.3/h vs. 0.3/h $p<0.005$) and snoring time (32% vs. 1%, $p<0.001$), as well as a worsening in sleep-related breathing parameters in the obese group.

Pien et al. [33] studied 105 women (mean BMI 33.4±6.4) during the first and third trimester of pregnancy. The mean AHI increased across gestation from 2.07 events/h to 3.74 events/h. BMI and maternal age at the beginning of pregnancy positively correlated with the occurrence of OSA in late pregnancy. Moreover, in a secondary analysis of the same cohort [34], including 123 women recorded in early and 97 also in late pregnancy, the authors reported a higher AHI (3.41±4.6 vs.

2.09±3.17) and a higher PLMS index (5.62±12.65 vs. 2.47±6.23) in late compared to early pregnancy. Also in this cohort, the increase in AHI was conceivably related to the increase in BMI, with values of 30.56±7.22 kg/m^2 in early vs. 33.3±6.25 kg/m^2 in late pregnancy ($p<0.001$).

Trakada et al. [43] studied 11 healthy pregnant women at 36 wk of gestation and again at 4–6 months postpartum with measurement of PaO2 every two hours. The AHI was significantly lower during late pregnancy compared to postpartum (5.81±2.1 vs. 12.1±2.7, $p<0.05$) with a longer mean duration of apneas/hypopneas in the postpartum period. The overall mean SaO2 (%) did not differ between the two time-points, but the mean PaO2 (%) in supine position was significantly lower in the antenatal period compared to the one in postnatal period (90.1±0.6 vs. 99.2±0.4, $p<0.001$). Edwards et al. [43] investigated 10 pregnant women (BMI 30±3 kg/m2) with OSA diagnosed in the third trimester with a second PSG 4 months after delivery (BMI 27±3 kg/m2). Women were treated with CPAP until delivery. The postnatal recordings showed consistent improvement of both AHI (63±15 vs. 18±4, $p=0.03$) and minimum SaO2 (86%±2% vs. 91%±1%, $p=0.01$) with reduced severity of blood pressure responses to apneas (170-180 mmHg vs. 130-140 mmHg), contrasting results of previous studies [43]. No significant relationship between changes in either weight or BMI from the antenatal to the postnatal sleep studies and changes in AHI were found.

3.2.3. Periodic limb movements during sleep (PLMS)

Few studies reported data on PLMS [28–30,34]. Most of them found no [28–30] or only a clinically non-significant increase [34] of the PLMS-Index measured across normal gestation or compared to non-pregnant controls.

Dzaja et al. [45] studied 10 pregnant women with RLS and 9 without RLS around the 36th week of gestation and 12 wk postpartum. Women with RLS showed more PLMS before ($F_{1,13}=6.11$, $p<0.05$) and after delivery ($F_{1,13}=3.21$, $p<0.1$) than controls. In particular, during pregnancy, PLMS were significantly more frequent in the RLS group in wake ($F_{1,13}=7.19$, $p<0.05$), S1 ($F_{1,13}=11.72$,

p=0.005), and S2 ($F_{1,13}$=4.87, p<0.05) sleep stage. Interestingly, subjects affected by RLS also had higher blood estradiol levels during pregnancy compared to controls. However, there was no correlation between PLMS index and RLS severity within the RLS group. Overall, PLM activity showed a negative correlation with estradiol levels in RLS patients (r=–0.66, p<0.05), but not in the control group (r=0.03, ns).

3.2.4. Subjective and other objective sleep assessment vs. polysomnography

Zhu et al. [23] analyzed the agreement between actigraphy and PSG in estimating basic key sleep parameters (TST, SE, WASO and SOL) of 38 healthy pregnant women during the third trimester. The best correspondence to PSG-derived parameters was obtained by using the 10 immobile/mobile minutes for sleep onset/end with an activity threshold of 10 (10-by-10), while the default scoring setting (10-by-40) provided significantly different results from the PSG (p<0.01).

By examining possible discrepancies between subjectively reported and objective PSG parameters in 33 women in the third trimester of gestation, 16 in the first trimester, and 15 non-pregnant women, Wilson et al. [46] found that the first group slightly overestimated TST, whereas the second and third groups tended to underestimate TST. Sleep latency was overestimated by all groups and corresponded closest to the first epoch of 10 minutes uninterrupted sleep or first epoch of SWS.

The same group later screened 380 pregnant women during the second trimester by means of the Berlin Questionnaire (BQ) and the Multivariable Apnea Risk Index (MAP-Index) [47]. Forty-three participants repeated the questionnaires and additionally underwent PSG at 37 wk of gestation, which in 15 cases (35%) showed an RDI>5/h. Overall, both the BQ and the MAP-index had low to moderate predictive value and were judged inadequate as screening instruments for SDB in pregnancy.

In a recent secondary analysis of their previous longitudinal study [33], Balserak et. al [48] tested the predictive value for OSA of the Sleep Apnea Symptom Score (SASS) vs. a combined model

incorporating questionnaire data with clinical measures, in 94 women not meeting the diagnostic criteria for OSA according to PSG in the first trimester of gestation. In the third trimester, 17 women (15.98%) had incident OSA (AHI≥5 events/h). The mean SASS administered in the first trimester showed acceptable validity and reliability to predict OSA. However, when adding maternal age, BMI, and bedpartner-reported information, the combined model performed better than the SASS alone in predicting OSA.

Finally, Sharkey et al. [49] and O'Brien et al. [50] tested the validity of two portable devices, compared to PSG, for the assessment of SDB during pregnancy. Both the Apnea Risk Evaluation System (ARES) [49] and the Watch-PAT-200 wrist-worn screening device [50] showed good sensitivity and specificity in the identification of SDB among pregnant women.

3.3. Polysomnographic findings in pregnancy-related complications

It is estimated that about 5% of all pregnancies are worsened by the occurrence of gestational complications, ranging from minor diseases to potentially life-threatening conditions for both mother and fetus [51].

Sleep disorders during pregnancy may play a role in inducing or exacerbating gestational complications, but these, in turn, may also deteriorate sleep. Few PSG studies addressed the topic of sleep in women affected by typical pregnancy-related complications, such as gestational hypertension (GHTN), preeclampsia (PE), and gestational diabetes (GDM), with the aim to shed more light on the bidirectional relationship between sleep and health problems occurring during pregnancy.

3.3.1. Hypertensive disease of pregnancy (HDP)

Three studies examined sleep in HDP. O`Brien et al. [52] studied 51 pregnant hypertensive women, of which 59% with chronic hypertension (CHTN), 23% gestational hypertension (GHTN) and 18% pre-eclampsia (PE), compared to 16 pregnant healthy women. Subjects belonging to the hypertensive group had a mean BMI>30 kg/m2 vs. 28.1±4.7 of the control subjects. Snoring was significantly more reported by hypertensive women (n=31; 61%) compared to controls (n=3; 19%). Snoring hypertensive women had a significantly higher AHI (19.9±34.1 vs. 3.4±3.1, p=0.013), a significantly lower SpO2% nadir (86.4±6.6 vs. 90.2±3.5, p=0.021) and were significantly more likely to have undiagnosed OSA (AHI≥5; 53% vs. 24%, p=0.03), than non-snoring hypertensive women. Thus, the authors pointed out that pregnant women presenting with a combination of hypertension and snoring are at risk of developing OSA with clinically significant oxyhemoglobin desaturation.

Reid et al. [53] investigated 34 obese pregnant women with GHTN, compared to 26 healthy pregnant women. SDB was significantly more frequent in the cases compared to the controls (53% and 12% respectively, p<0.001). Nocturnal blood-pressure monitoring showed no group specific differences in hemodynamic response to respiratory events including flow limitations, contrasting the results from another recent study by Edwards et al. [54]. However, in both groups, upper airway obstructive events of any severity were associated with a substantial transient blood pressure response, as shown by a later secondary analysis of the dataset [55].

Wilson et al. [56] compared obese women with HDP with normotensive pregnant controls matched for BMI, age and gestational age. SDB was found to be more common (52.5% vs. 37.5%) and more severe (35% vs. 15% of subjects with RDI>10/h, p=0.039) in the HDP vs. control group, although RDI did not differ (p=0.20) between groups.

3.3.2. Pre-eclampsia (PE)

Four studies examined the sleep pattern of women with PE. Edwards et al. [57] performed third trimester PSG in 25 women suffering from PE and 17 healthy pregnant control subjects. Pre-eclamptic patients showed an increase in SWS (43±3% vs. 21±2%, $p<0.001$), a longer REM sleep latency (205±23 vs. 92±11 min, $p<0.001$) and a reduced REM-sleep percentage (10±2% vs. 18±1%, $p<0.001$). REM-related sleep changes were possibly due to clonidine medication in the patient group.

In a later study, the same authors performed PSG in pregnant women in the third trimester suffering from OSA (n=10) or both OSA and PE (n=10) [54]. Blood-pressure responses to obstructive respiratory events during sleep were significantly increased in patients affected by both conditions, compared to normotensive OSA patients. No significant difference between groups in heart rate response was found, but, as compared to control OSA patients, heart rate did not show any modification during sleep and wakefulness in PE patients, suggesting a possible alteration in the normal pattern of reduced sympathetic tone during NREM sleep in this group.

Guilleminaut et al. [58] performed PSG in 12 women with risk factors for PE (hypertension, obesity and prior PE). None of them had oxygen desaturations >3% but all participants showed significant SDB (mean RDI 8.5±2.6). All women received nasal CPAP treatment for the remainder of pregnancy, which was effective in alleviating SDB symptoms and ameliorating blood pressure control in patients with pre-existing hypertension, but did not prevent negative pregnancy outcomes associated with obesity and PE.

Suri et al. [59] conducted a prospective PSG study in 40 patients with PE or GHTN aged 25.3±3.9 years (mean GA 34.9±1.7 wk) and 60 healthy pregnant controls aged 25±3.5 years (mean GA 35.7±2.0 wk). Pre-pregnancy and present BMI, as well as AHI, snoring, systolic (SBP), diastolic (DBP), and mean (MBP) blood pressures were significantly higher in cases than in controls. SDB

was more frequent (p=0.018; OR 13.1) and more severe (p=0.001; OR 1.8) in hypertensive pregnant women vs. healthy pregnant women, even after controlling for pre-pregnancy BMI. AHI was significantly associated with blood pressure, even after adjustment for BMI. Therefore, the authors concluded that not only obesity may play a role in the causation of hypertension and SDB, but also SDB may be implicated in the development of hypertension (r=0.612; p=0.01).

3.3.3. Hyperglycemia and gestational diabetes mellitus (GDM)

Three studies examined sleep in women with GDM. Reutrakul et al. [60] analyzed PSG features of healthy pregnant women, pregnant women with GDM and non-pregnant healthy controls (n=15 individuals for each group). When comparing pregnant women with and without GDM, the first group showed a lower TST (median 397 vs. 464 min, p<0.02), a higher AHI (median 8.2 vs. 2.0, p<0.05) and a higher prevalence of OSA (73% vs. 27%, p<0.01). In multivariate analysis, after adjusting for pre-pregnancy BMI, the diagnosis of OSA was associated with GDM (OR 6.60). In pregnant women, a higher AI was significantly associated with higher HbA1c and fasting glucose levels, which, in turn, were positively associated with ODI.

By contrast, Bisson et al. [61], evaluating sleep characteristics of pregnant women with and without GDM, found no statistically significant differences between groups regarding sleep structure, breathing variables, and movement parameters.

In their large prospective PSG study, Izci Balserak et al. [62] examined the correlation between SDB and glucose tolerance (measured with OGTT at enrolment) in a cohort of 104 pregnant women, recorded in the first and third trimester (83 women). No differences in sleep structure and breathing parameters were found between the hyperglycemia (GCT≥135, n=11) and normoglycemia (GCT<135, n=93) groups. Although RDI and flow-limitations were not reported, symptoms of SDB (snoring 9.3% vs. 45.5%, p<0.01; daytime nap duration 1.49±1.3 hr vs.

2.27±1.4, p=0.07; MAP-index 0.52±0.8 vs. 1.53±1.1, p<0.01) rather than objective breathing parameters were associated with maternal impaired glucose tolerance.

3.3.4. Adverse fetal outcomes

Sahin et al. [63] performed third trimester PSG in 35 healthy pregnant women who reported frequent snoring. Among the four women, who were found to suffer from OSA (mean BMI 37.5±8.4, mean AHI 13.5±5.5), two also had GDM and one cardiovascular disease. Three of them showed fetal heart deceleration accompanying maternal desaturation and their neonates had lower APGAR scores, as well as birth weights compared to those from women without OSA.

More recently, Pamidi et al. [64] explored the relationship between PSG-diagnosed SDB in the third trimester of pregnancy and delivery of small for GA infants (defined as growth <10th percentile for the corresponding GA) in a prospective cohort study of 234 women. Twenty-seven (12%) women delivered a SGA infant. SDB symptoms in the third trimester were found to be not predictive of delivering an SGA baby and their overall sensitivity and specificity for predicting a PSG-based diagnosis of SDB was also poor. By contrast, a PSG-based diagnosis of SDB in the third gestational trimester was associated with a significantly increased odds of delivering an SGA baby (using a AHI cut-off of 10 events/h, OR 2.65).

In their prospective study, Fung et al. [65] investigated the effects of maternal OSA on fetal growth. Of 371 screened women, 41 patients (n=26 high-risk and n=15 low-risk) underwent PSG during the second trimester and subsequent fetal growth assessment in the third trimester. Fourteen women received a PSG-confirmed diagnosis of OSA (RDI>5/h). The remaining 27 subjects represented the control group. Impaired fetal growth was observed in 43% of cases, vs. 11% of non-OSA controls (RR 2.67; 1.25–5.7; p=0.04). Logistic regression analysis identified OSA (OR 6; 1.2–29.7, p=0.03) and BMI (OR 2.52; 1.09–5.80, p=0.03) as significant predictor of fetal growth restriction. However,

when adjusting for BMI in multivariate analysis, the association did not reach statistical significance (OR 5.3; 0.93–30.34, p=0.06).

Finally, Kneitel et al. [66] compared women without OSA or treated with PAP-therapy in a retrospective case-control setting. There was no difference between the percentage of infants with growth restriction (small for GA, <10th percentile) from women with or without OSA, although in logistic models the presence of OSA was predictive of slowing fetal growth in the third trimester.

3.4. Interventional approaches in pregnancy

3.4.1. CPAP during pregnancy

As for non-pregnant women, CPAP is generally considered the first-line therapy for pregnant women affected by OSA. Three studies objectively assessed the effects of CPAP on sleep during pregnancy.

Guilleminaut et al. [67] treated 12 women with OSA with nasal CPAP (mean AHI 21 events/h, mean RDI 33 events/h). Full PSG was performed at study entry, during CPAP titration, and repeated at 6 months of gestation (GA). An additional home monitoring of cardio-respiratory variables was conducted at 8 months GA. From the first to the second PSG recording, a moderate worsening of PLM score and snoring was noted in three women, and CPAP pressure had to be increased in six cases. Subjective measures of sleepiness, fatigue and snoring improved significantly compared to study entry and CPAP showed overall a good compliance and safety.

Blyton et al. [68] studied the effect of CPAP treatment on blood pressure, heart rate and cardiac stroke volume in 24 women with severe PE, who were randomly assigned to either receive nasal

CPAP (n=12) or no treatment (n=12). PSG was performed on two consecutive nights (baseline and treatment). Objective sleep features were compared between groups and to a healthy pregnant control group (n=15). The amount of REM sleep (%) was reduced in PE women regardless of treatment status compared to control subjects (23±3, 12±6, and 12±7% of TST in control, no-CPAP, and CPAP subjects, respectively, $p<0.001$). The RDI was slightly increased in both PE groups compared to control subjects (9±4 events/h, 19±10 events/h, and 22±23 events/h in control, non-CPAP, and CPAP subjects, respectively, $p=0.10$) and all cases showed upper-airway flow limitations. pre-eclamptic women had increased daytime blood pressure, a reversed nocturnal BP decrement and a significantly lower heart rate in NREM, as well as a significant decrease of cardiac stroke volume during sleep compared to control cases. Furthermore, total peripheral resistance was heightened, and cardiac output reduced. All the above-mentioned variables improved or normalized with CPAP treatment.

The same authors [69] also performed third trimester PSG in 20 women with PE and 20 healthy pregnant women (BMI 31.9±3.2 vs. 30.6±2.5 kg/m2, $p=0.15$). Preeclamptic patients showed significantly more flow limitations, higher AHI and increased number of oxygen desaturation especially during REM sleep, compared to controls. Fetal wellbeing, measured by movement pattern and hiccups, was also significantly reduced in PE patients and responded to CPAP.

3.4.2. Positional therapy

In the third trimester, the majority of pregnant women spend up to 25% of TST in supine position [70–72], which is considered to be a risk factor for still births (SB), with an attributable risk of between 3.7% and 37% [73,74]. Avoiding supine position during sleep in pregnant women could therefore significantly reduce the occurrence of late SB.

Kember et al. [75] performed a two-night, in-lab, PSG study with a cross-over design in 20 pregnant women in the third trimester, in order to evaluate the effect of a positional therapy device

(PrenaBelt), compared to a sham device, in discouraging healthy pregnant women to sleep in supine position. Considering all available recordings (n=40 nights), the median percentage of sleep time spent in supine position was reduced from comparable low baseline values of 16.4% on the sham night to 3.5% on the PrenaBelt night (p=0.03), with overall good compliance and tolerability. Sleep macrostructure and sleep-related breathing and movement parameters did not significantly differ between groups and remained within the normal range, as expected in this low-risk population.

3.5. Quantitative analysis (meta-analysis)

Five studies reporting TST and six reporting SE were selected for inclusion in the meta-analysis. Results are presented as forest plots in figure 2 and 3. TST was overall significantly reduced from the first to the third trimester of pregnancy by 26.8 min (pooled WMD, 95% CI=12.14-41.56). Similarly, SE was reduced between first and third trimester by 4% (pooled WMD, 95% CI=1.50-6.65). A significant statistical heterogeneity between studies was found for both sleep parameters evaluated (I^2>50%). Egger's test detected no significant publication bias for studies reporting TST (p>0.1), but a possible publication bias for studies reporting SE (p=0.072).

4. Discussion

Changes in sleep structure during pregnancy, as objectively measured by PSG, mainly consist in a reduction of sleep duration (TST), due to an increase of WASO, and in a transition from N3 and REM sleep to more superficial NREM sleep stages (N1, N2) [28,29]. As a result, mean SE is diminished and sleep is perceived as non-restorative across gestation [30].

These findings become particularly evident in the third trimester and are confirmed both by studies comparing pregnant with age-matched non-pregnant women, and by a recent large analysis of PSG data collected among the same mothers during early and late pregnancy [34].

Hormonal variations can only partially explain these alterations, which should instead be ascribed to a series of concurrent factors, including anatomical/mechanical changes and psychological variables [31].

Objective sleep alterations occurring during pregnancy are precisely detected by PSG and might be relevant in guiding appropriate therapeutic strategies for women reporting poor sleep quality and insomnia symptoms across gestation. Previous research has shown that, in untreated women, actigraphy-assessed sleep variables tend to worsen from pregnancy to postpartum [76] and that cognitive behavioral therapy for insomnia (CBT-I) can significantly reduce insomnia symptoms and improve objectively measured sleep variables, such as SE, SOL, and TIB in pregnant women [77]. However, since objective TST seems to be not significantly modified by CBT-I [77], the benefits of using this treatment during pregnancy need to be further studied and evaluated.

According to the PSG studies published so far, there is poor evidence of an increased occurrence of SDB among healthy, normal-weight pregnant women without risk factors, suggesting that pregnancy per se does not necessarily predispose to major changes in sleep-related respiratory parameters. However, a deterioration of the respiratory pattern during pregnancy, with a higher AHI, ODI, snoring time and incidence of OSA, particularly in the third trimester, is generally a common finding in studies analyzing SDB in at-risk pregnant women. Besides gestational age, some pre-existing conditions, such as a BMI in the range of obesity, a larger neck circumference, as well as higher maternal age at pregnancy onset, should be carefully considered as possible risk factors for the development of OSA during pregnancy [33,34,75].

Also, in most studies, the classical PSG parameters considered for diagnosing OSA in the non-pregnant population, such as AHI and ODI, show no significant differences or are only slightly increased, without reaching a pathological threshold (i.e. AHI≥5) in pregnant women [38]. This raises the question whether the current diagnostic criteria for OSA also apply to pregnancy, and whether other respiratory markers, such as airflow limitations and snoring, may be more reliable in identifying possible borderline pathological conditions, which may predispose to pregnancy-related

adverse cardiovascular or other health outcomes [40]. Future research should be therefore focused on better defining normative PSG values for SDB during pregnancy based on large datasets.

The frequency and characteristics of PLMS during pregnancy are clearly underinvestigated, but the available studies did not show a relevant increase of PLMS-Index in women across gestation or compared to non-pregnant controls. This is a surprising finding, considering the high prevalence of RLS during pregnancy [78] and that up to 80% of patients with RLS also have increased PLMS [79]. In fact, the only small PSG study examining pregnant women with RLS confirmed these to have more PLMS before and after delivery than healthy pregnant controls [45].

Subjective tools to evaluate sleep characteristics or to screen for SDB in pregnant women must be carefully interpreted, due to their generally lower accuracy compared to PSG. Some of these instruments may be implemented by adding information provided by the women themselves or their bed partners, which may critically improve the sensibility of the tools [47,48]. This suggests that the creation and validation of new questionnaires specifically targeting the pregnant population are recommended for future research studies.

Actigraphy represents a valid objective alternative to PSG for assessing some fundamental sleep parameters, such as TST, SE or WASO. However, its accuracy in comparison to PSG seems to be clearly influenced by the basic settings of the devices used, which would require to be validated during pregnancy [23], paying particular attention to the late GA, when mobility is reduced.

Single validation studies of a few portable devices for detecting SDB in pregnant women have shown a good diagnostic sensibility of these instruments with respect to PSG [49,50].

Hypertensive disorder of pregnancy (HDP), independently from its nature, is associated with snoring, and women affected by both conditions are more likely to have a higher AHI and to suffer

from OSA [52]. Moreover, obesity may play a significant role in predisposing pregnant women with HDP to develop SDB and BMI should be therefore carefully accounted for when evaluating pregnant hypertensive individuals.

Pregnant women affected by PE not only show alterations of sleep structure, with increased SWS and REM sleep latency, as well as reduced REM sleep percentage, but are also more likely to suffer from snoring and SDB. In particular, PE patients have a higher AHI, AI, and a lower minimum oxygen desaturation, which all positively correlate with blood pressure parameters, even after adjustment for BMI, and predispose to poor maternal and fetal outcomes [58].

Data regarding the association between gestational diabetes and altered sleep pattern or SDB are scarce and not consistent. However, the largest study on maternal hyperglycemia conducted so far showed that, also in this case, the traditional parameters used to diagnose SDB may not differ between patients and healthy control subjects, even if symptoms of respiratory disturbances during sleep may be significantly more frequent in patients with impaired glucose tolerance [62].

A few studies examined the association between OSA and severe perinatal outcomes, such as impaired fetal growth or newborns small for gestational age (SGA). In particular, a PSG-based diagnosis of SDB in the third gestational trimester was associated with a significantly increased odds of delivering an SGA baby [64]. However, BMI seems, once again, to critically influence the value of OSA as predictor of fetal growth restriction [80]. In general, further evidence especially regarding the role of mild OSA as risk factor for pregnancy-related complication, as well as the efficacy of CPAP therapy in preventing such complications is warranted.

To date, interventional studies evaluating the effects of CPAP on pregnancy-related OSA and PE by using PSG are lacking, but overall supporting the use of this type of non-invasive ventilation, which is generally well tolerated and remarkably contributes to improve subjective sleep quality and daytime symptoms, as well as objective sleep and hemodynamic parameters [67,68].

Some limitations of the present analysis should be considered. First, some studies only report parts of their polysomnographic results, generally those addressing the specific research question, or possibly only the positive ones. Also, main characteristics considerably differ between studies, e.g. regarding design, population, sample size, time of pregnancy and criteria used for PSG scoring. This large heterogeneity makes it difficult to draw definitive conclusions about most outcome parameters and to pool the data in order to perform meta-analysis.

Finally, articles reporting PSG results from a sample < 10 women, as well as reduced montage polygraphic studies (without EEG, EMG and EOC derivations) were excluded from the present review. Although PSG is the most accurate method for sleep depiction, its use in the clinical setting may be complicated by the limited availability, the necessary technical equipment, and the elevated costs. Also, it must be considered that PSG data obtained from a single recording might be biased by an habituation effect (also called "first night effect"), especially if the sleep study was not performed in the home environment [81].

In conclusion, growing PSG studies are providing further knowledge on the intrinsic features of sleep during pregnancy, thus contributing to better describe changes in objective sleep variables occurring in pregnant women beyond subjective reports. Portable devices will help collecting large-scale data in future research, but efforts are needed in designing more homogenous and comparable studies, in order to maximize the information gained from the results and to better understand the clinical value of using PSG during pregnancy.

Practice Points

Sleep disturbances during pregnancy are common and may sometimes require a full polysomnographic assessment in order to:

1. correctly identify pregnancy-related sleep disorders according to current diagnostic criteria

Research Agenda

Future research studies using polysomnography in pregnant women should be preferably aimed at:

1. evaluating changes in sleep variables within the same women at different time points before, during, and after pregnancy by adopting longitudinal study designs
2. establishing an expert consensus on the minimal polysomnographic parameters to be reported in studies on pregnancy and on the sleep scoring criteria to be adopted
3. creating large datasets in order to define normative polysomnographic values per each trimester of pregnancy
4. developing algorithms based on combined information from PSG and questionnaires, in order to better predict pregnancy-related clinical outcomes
5. further validating the accuracy of portable polygraphy devices vs standard polysomnography.
6. evaluating the efficacy of CBT-I and CPAP in treating respectively insomnia and sleep disordered breathing during pregnancy

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Figure 2: Forest plot of studies reporting TST included in meta-analysis

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Supplementary material

Table S1: PRISMA checklist

Table S2: Quality assessment of the studies included in the systematic review

Table S3: Main characteristics of controlled studies

Table S4: Main characteristics of non-controlled studies

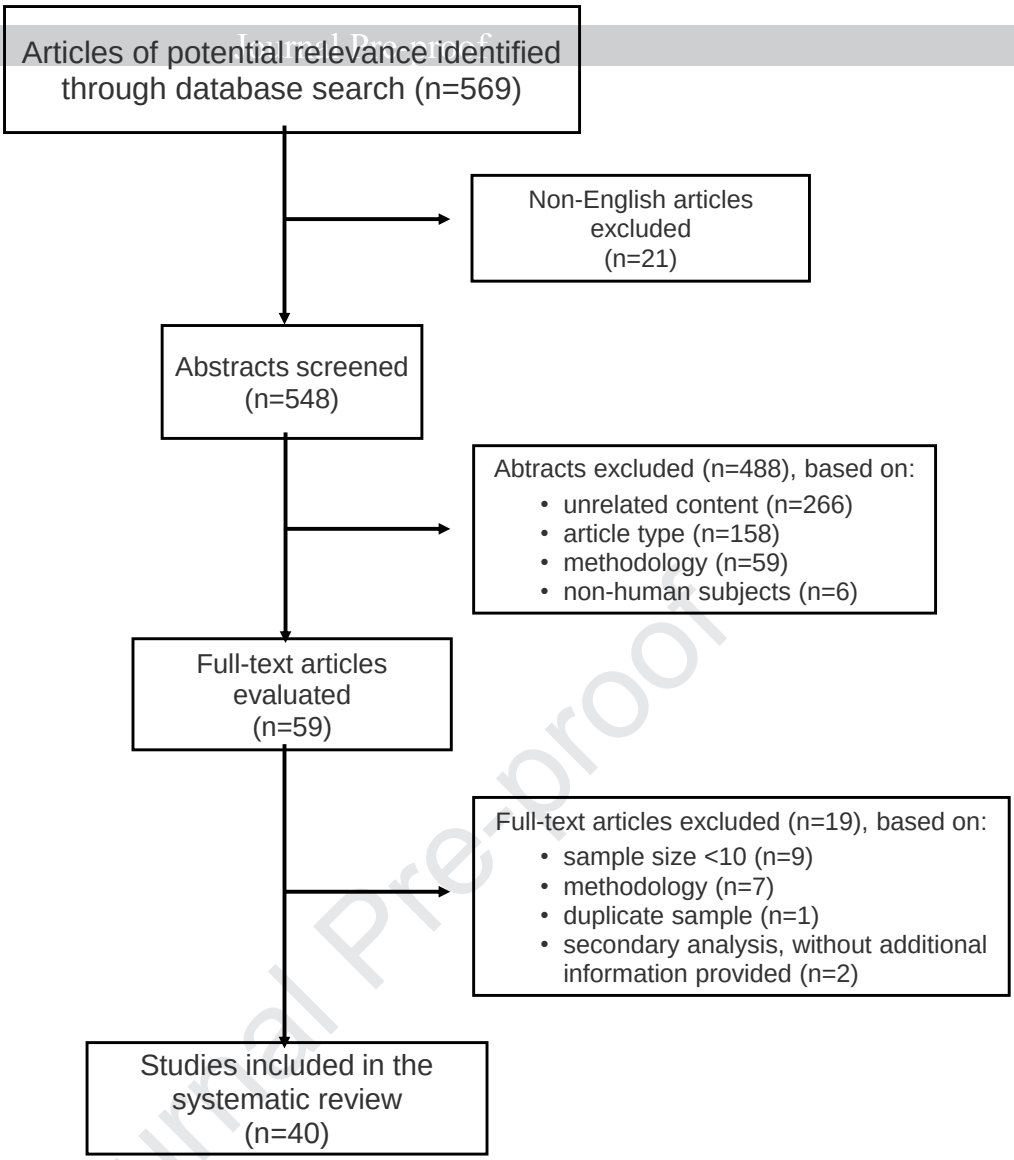
Table 1: Changes in sleep variables in pregnancy and pregnancy-related complications.

AUTHORS	*YEAR*	*TYPE OF PATIENTS EVALUATED*	*GA (in weeks)*	*CHANGE IN SLEEP VARIABLES IN CASES IN RESPECT TO CONTROLS/CONTROL CONDITIONS*									
				TST	*SE*	*AI*	*SL*	*REM*	*SWS*	*RDI*	*AHI*	*ODI*	*OSA%*
Healthy pregnancy													
Izci-Balserak et al.[34]	*2018*	Healthy pregnant women in the first (controls) compared to the third trimester (cases).	12.05 ± 1.80 (controls) 33.61 ± 2.56 (cases)	↓	↓	↔	↔	↓	↓		↑		↑
El-Helbawy et al.[39]	*2017*	Healthy pregnant women (cases) and healthy non-pregnant women (controls).	23.03 ± 8.88 (cases)								↑	↑	
Rimpilä et al.[29]	*2017*	Healthy pregnant women (cases) and healthy non-pregnant women (controls).	33 ± 1	↓	↓		↔	↓	↓		↔	↔	
Wilson et al.[30]	*2011*	Pregnant women in the first and third trimester of pregnancy (cases) and healthy non-pregnant controls (controls).	Controls and first trimester (9 – 14) vs. third trimester (30 – 38)		↔	↑	↔	↔	↔				↑
			Controls vs. third trimester (30 – 38)		↓		↔	↓	↓				↑
Trakada et al.[43]	*2003*	Healthy pregnant women pre- (cases) and postpartum (controls).	36 (cases) 4–6 months PP (controls)	↔	↔	↔		↔	↔				
Lee et al.[32]	*2000*	Healthy women pre-, during and after pregnancy.	Pre-pregnancy (controls) 11-12 (cases)	↑	↓		↔	↔	↓				
			3-4 weeks PP (controls) 35-36 (cases)	↑	↑		↔	↔	↓				
Hertz et al.[28]	*1992*	Healthy pregnant women (cases) and non-pregnant healthy women (controls).	30-38	↔	↓		↔	↓	↔				
Hypertensive disorders of pregnancy													
Suri et al.[59]	*2018*	Pregnant women with PE and/or GH (cases) and healthy pregnant women (controls).	34.9 ± 1.7 (cases) 35.7 ± 2.0 (controls)			↑					↑		↑

AUTHORS	*YEAR*	*TYPE OF PATIENTS EVALUATED*	*GA (in weeks)*	*CHANGE IN SLEEP VARIABLES IN CASES IN RESPECT TO CONTROLS/CONTROL CONDITIONS*									
				TST	*SE*	*AI*	*SL*	*REM*	*SWS*	*RDI*	*AHI*	*ODI*	*OSAS*
Wilson et al.[56]	*2018*	Pregnant women with GH/PE (cases) and healthy pregnant women (BMI and GA match, controls).	33.5 ± 3.4 (cases) 33.1 ± 2.4 (controls)	↔	↔	↔	↔	↓	↔	↔	↔	↔	↑
Reid et al.[55]	*2016*	Pregnant women with GH (cases) and healthy pregnant women (controls).	34.2 ± 3.3 (cases) 34.5 ± 3.2 (controls)	↓	↔	↔		↓		↑	↔		
O'Brien et al.[52]	*2014*	Pregnant women with chronic HT, GHT and PE (cases) and healthy pregnant women (controls).	24.6 ± 8.1 (cases, cHT) 33.0 ± 2.9 (cases, GHT) 30.1 ± 4.2 (cases, PE) 33.8 ± 3.8 (controls)	↔							↔		↑
Blyton et al.[69]	*2013*	Pregnant women with PE (cases) and healthy pregnant women (controls).	33.3 ± 3.5 (cases) 33.9 ± 2.0 (controls)	↔		↔		↔	↑		↑	↔	
Reid et al.[53]	*2011*	Pregnant women with GH (cases) and healthy pregnant women (age and GA match, controls).	34.7 ± 3.2 (cases) 34.7 ± 2.6 (controls)	↓	↓	↔		↓	↔	↑	↑	↔	↑
Blyton et al.[68]	*2004*	Pregnant women with PE (cases), 50% with CPAP, and healthy pregnant women (controls).	33 ± 4 (cases) 34 ± 2 (controls)	↔				↓		↔			
Edwards et al.[54]	*2001*	Pregnant women with OSAS and PE (cases) and normotensive pregnant women with OSA (controls).	34 ± 1 (cases) 32 ± 2 (controls)	↔		↔		↔		↔			
Edwards et al.[57]	*2000*	Pregnant women with PE (cases) and normotensive healthy pregnant women (controls).	33 ± 1 (cases) 34 ± 1 (controls)	↔	↔	↔	↔	↓	↑	↔			
Gestational diabetes mellitus													
Bisson et al.[61]	*2014*	Pregnant women with newly diagnosed GDM and BMI ≤ 35 (cases) and healthy pregnant women matched for GA, BMI and age (controls).	31.6 ± 1.4 (cases) 32.3 ± 1.0 (controls)	↔	↔	↔	↔	↔	↔		↔	↔	↔
Izci Balserak et al.[62]	*2013*	Healthy pregnant women stratified for the presence (cases) and absence (controls) of GDM, PSG in first trimester and third trimester.	12 ± 2.1	↔		↔					↔		
			3rd trimester	↔		↔					↔		

AUTHORS	*YEAR*	*TYPE OF PATIENTS EVALUATED*	*GA (in weeks)*	*CHANGE IN SLEEP VARIABLES IN CASES IN RESPECT TO CONTROLS/CONTROL CONDITIONS*									
				TST	*SE*	*AI*	*SL*	*REM*	*SWS*	*RDI*	*AHI*	*ODI*	*OSAS*
Reutrakul et al.[60]	*2013*	Pregnant women with GDM (cases), healthy pregnant women (controls).	33.3 ± 3.5 (cases) 33.9 ± 2.0 (controls)	↓		↔		↔	↔		↔	↔	
		Healthy pregnant women (cases) and healthy non-pregnant women (controls).	33.9 ± 2.0 (cases)	↔		↑		↓	↔		↑	↔	
Clinically suspected OSAS or risk factors for OSAS													
Bourjeily et al.[40]	*2014*	Pregnant women with suspected OSAS (cases) and healthy non-pregnant women matched for age, BMI and AHI (controls).	26.6 ± 7.6 (cases)	↓	↔	↔	↔	↔	↓	↔	↔		
Edwards et al.[44]	*2005*	Pregnant women with suspected OSAS (cases) and postpartum (controls).	33 ± 2 (cases) 4 ± 2 months PP (controls)	↔	↑		↑	↓	↑		↑		
Maasilta et al.[42]	*2001*	Obese pregnant women (cases) and normal-weight healthy pregnant women (controls).	≥ 12	↔	↔	↑	↔	↔	↔	↑	↑	↑	
			≥ 30	↔	↔	↑	↔	↔	↔	↑	↑	↑	
Guilleminault et al.[38]	*2000*	Pregnant women with chronic snoring and/or SaO2 drop ≥ 5 % in a screening examination (cases), and healthy pregnant women matched for age and BMI (controls).	24	↔					↑		↔		
Restless legs syndrome													
Dzaja et al.[45]	*2009*	Pregnant women with RLS (cases) and healthy pregnant women (controls).	35.9 ± 1.9 (cases and controls)	↔			↔	↔	↔				

Legend: AHI – apnea/hypopnea index, AI – arousal index, BMI – body mass index, cHT – chronic hypertension, C-PAP – continuous positive airway pressure, GA – gestational age, GH – gestational hypertension, GDM – gestational diabetes mellitus, ODI – oxygen desaturation index, OSA – obstructive sleep apnea, PE – pre-eclampsia, RDI – respiratory disturbance index, REM – rapid-eye-movement sleep, RLS – restless legs syndrome, TST – total sleep time, SE – sleep efficiency, SL – sleep latency, SWS – slow-wave sleep,



Study	Year	N 1st trimester	N 3rd trimester	Mean difference	Approximate 95% CI	
Izci-Balserak et al.[34]	2018	123	97	14,08	-1,933734	30,093734
Izci-Balserak et al.[62]	2013	93	75	28,8	16,453324	41,146676
Maasilta et al.[42]	2001	11	11	52	32,13489	71,86511
Lee et al.[32]	2000	33	29	31	-1,444177	63,444177
Coble et al.[31]	1994	20	18	3	-27,035781	33,035781

Random effects (DerSimonian-Laird):

Pooled weighted mean difference =
26.857772 (95% CI = 12.148938 to 41.566606), Z = 3.57882, P = 0.0003

Heterogeneity: Cochran's Q = 11,006579 (df = 4) P = 0,0265, I^2 = 63,7%

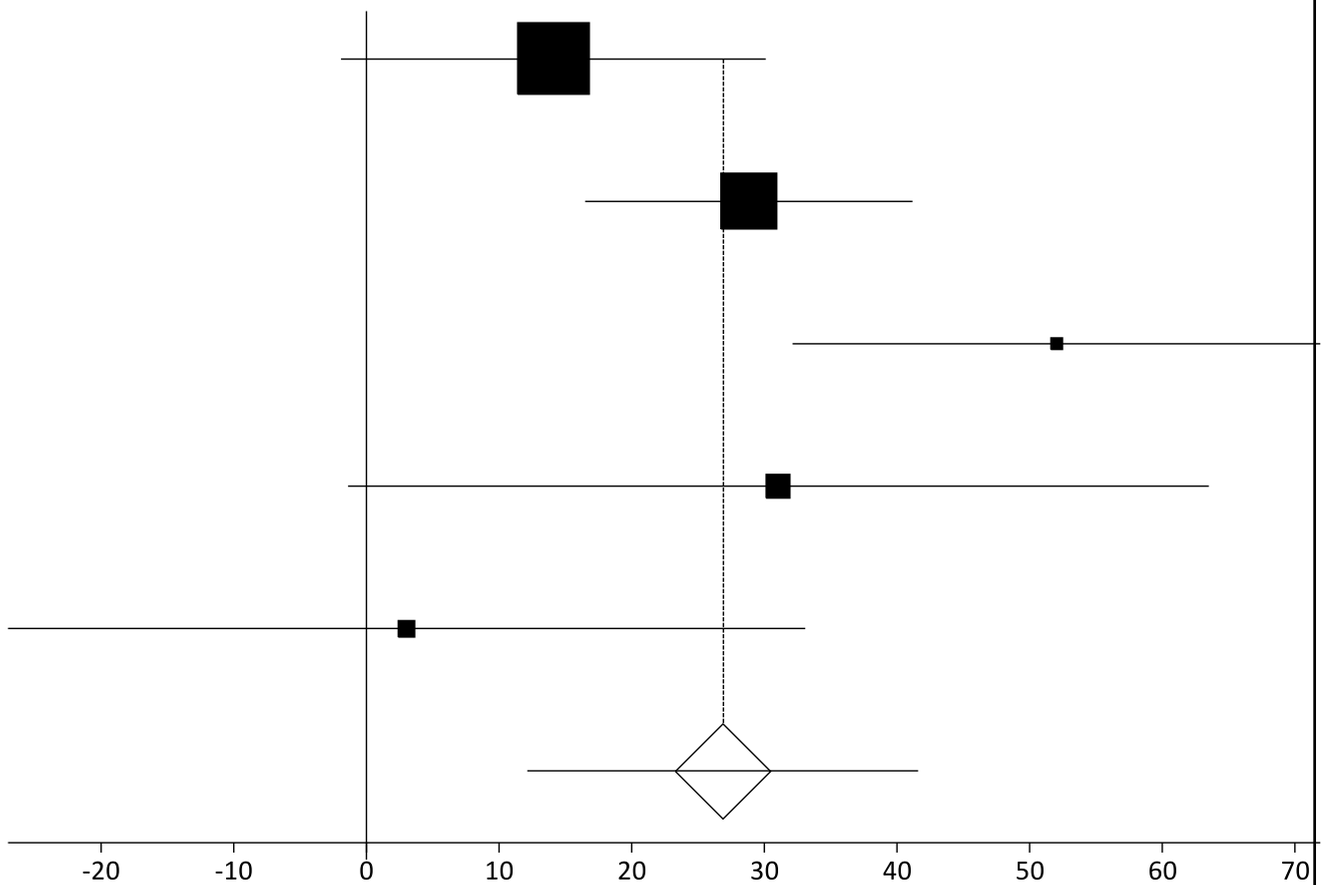
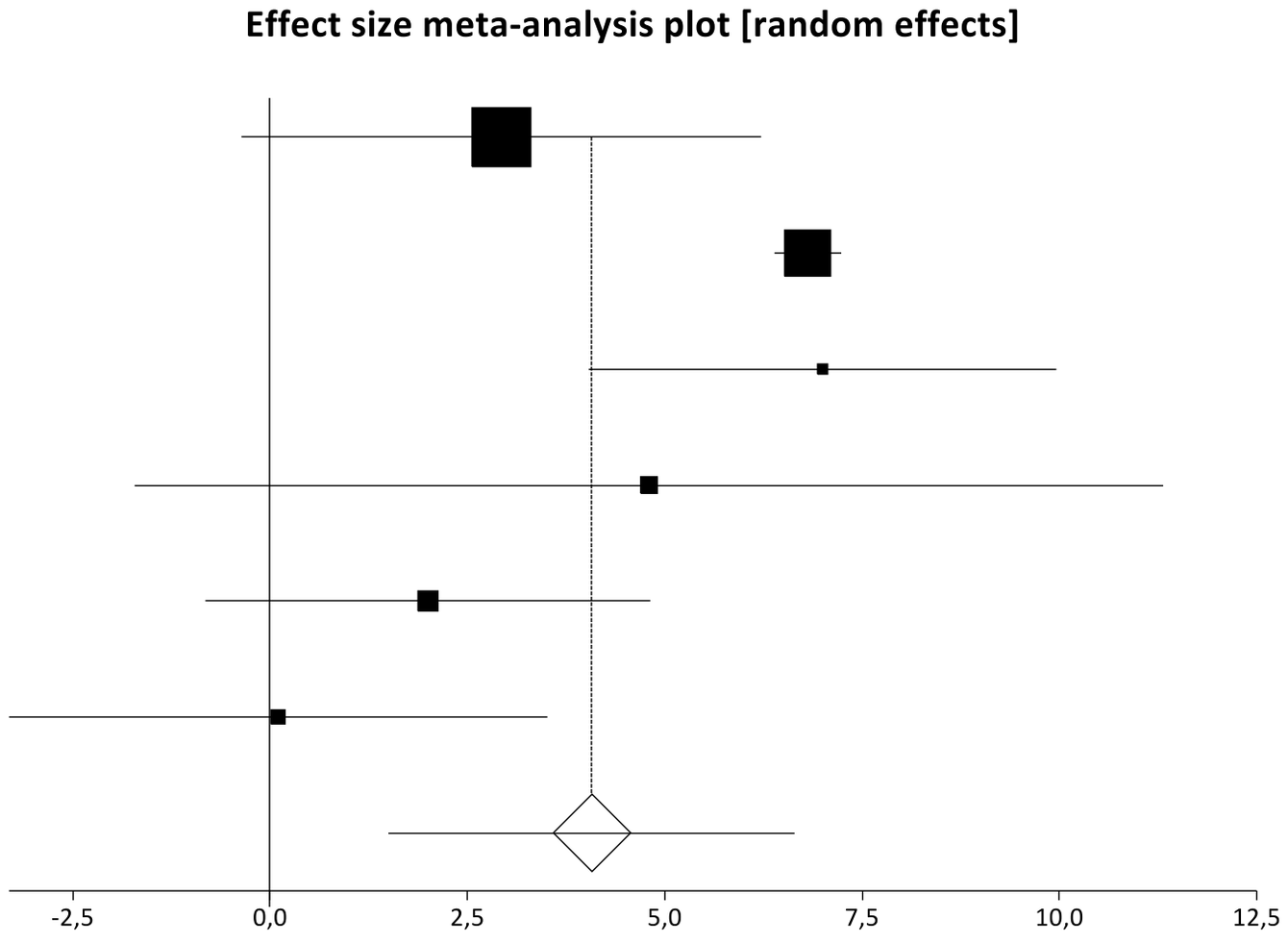


Fig. 2. Forest plot of weighted mean difference (WMD) in total sleep time (TST) between first and third trimester of pregnancy in minutes. WMD higher than 0 indicates longer TST in the first vs. third trimester of pregnancy.

Study	Year	N 1st trimester	N 3rd trimester	Mean difference	Approximate 95% CI	
Izci-Balserak et al.[34]	2018	123	97	2.93	-0,356561	6,216561
Izci-Balserak et al.[62]	2013	93	75	6.81	6,383767	7,236233
Maasilta et al.[42]	2001	11	11	7	4,045243	9,954757
Wilson et al.[30]	2011	21	27	4.8	-1,722925	11,322925
Lee et al.[32]	2000	33	29	2	-0,814621	4,814621
Coble et al.[31]	1994	20	18	0.1	-3,308535	3,508535



Random effects (DerSimonian-Laird):

Pooled weighted mean difference =
4.078768 (95% CI = 1.50716 to 6.650376), Z = 3.108653, P = 0.0019

Heterogeneity: Cochran's Q = 29,40515 (df = 5) P < 0,0001, I^2 = 83%

Fig. 3. Forest plot of weighted mean difference (WMD) in sleep efficiency (SE) between first and third trimester of pregnancy in percent. WMD higher than 0 indicates a higher percentage of SE in the first vs. third trimester of pregnancy.