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ORIGINAL ARTICLE

Sleep spindle characteristics in overweight adolescents with obstructive sleep apnea syndrome

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Abstract Sleep spindles may display a sleep protective function. Thus, their activity is also a stable marker of sleep disturbances. We investigated whether spindle activity could be altered in overweight (OW) adolescents with obstructive sleep apnea syndrome (OSAS), compared with OW controls and normal weight (NW) adolescents. We also evaluated spindle characteristics correlation with body mass index (BMI) and OSAS-related sleep parameters. Thirty OW adolescents and 15 NW adolescents (age 14–17 years; all males) underwent polysomnography. Sleep spindles were automatically detected during stage 2 non-rapid eye movement sleep. The spindle activity characteristics involved: number of spindles; mean spindle density; mean maximum spindle amplitude; mean spindle duration; and mean spindle frequency. All adolescents were divided into three groups (18 OW patients with OSAS, 12 OW controls and 15 NW controls). Number of spindles and spindle density were significantly higher, but maximum spindle amplitude and spindle frequency were significantly lower in OSAS patients, as compared in both OW controls and NW controls. In this group, significant correlations were also found between spindle characteristics and OSAS-related sleep parameters (apnea hypopnea index, min SaO_2 and total arousal index), but no significant correlations were found between spindles and BMI. The increased spindle number and spindle density in OW adolescents with OSAS might be the EEG responses to multiple brief occlusions or loads applied during inspiration in impaired sleep, an adaptive response to sleep fragmentation and hypoxia.

Keywords Adolescents · Obstructive sleep apnea · Body mass index · Spindles

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Introduction

It is known that sleep spindles are composed of transient electroencephalography (EEG) oscillations in the frequency range of 11–16 Hz, lasting at least 0.5 s [1]. Sleep spindles are well known to sleep investigators as the EEG-hallmarks of stage 2 (S2) non-rapid eye movement (NREM) sleep. Animal and human studies converge to demonstrate that sleep spindles are generated through the interplay between specific populations of thalamic (particularly thalamic reticular) and cortical neurons [2, 3]. It has been suggested that sleep spindles may gate synaptic transmission through the thalamus to the cortex and thereby display a sleep protective function. Spindles may play an active role in inducing and maintaining sleep. Studying the sleep spindle patterns could provide an additional, sensitive tool to indicate insufficient or disturbed sleep [4].

Obstructive sleep apnea syndrome (OSAS) is associated with repetitive episodes of upper airway obstruction during sleep and results in oxygen desaturation and arousals from

sleep [5, 6]. Childhood obesity is a major risk factor for OSAS, and the likelihood of an obese child developing OSAS is 4–5 times greater than in a nonobese child [7]. Conversely, school-aged children are at risk of developing future obesity if they sleep less than 9 h per night or if they have OSAS [8, 9]. Several recent studies have shown an association between obesity and OSAS during the important developmental transition phase of adolescence [10, 11]. Limited studies have examined the sleep spindle patterns in OSAS, and none have evaluated those in obesity. So, it is known, that in adult OSAS patients, spindle density and frequency decreases, the percentage of slow spindles increases, and the spindles remain slow throughout the night [12]. Since OSAS is a known cause of brain dysfunction [13] and obesity is the result of diencephalic-cortical network integrity disturbance [14], OSAS- and obesity-associated spindle abnormalities are interesting to study together. However, no pediatric studies have assessed sleep spindles in overweight (OW) adolescents with OSAS.

We hypothesized that sleep spindle process would be disturbed in OW adolescents with OSAS. Therefore, the purpose of this study was to perform sleep spindle analysis in a group of OW adolescents affected by OSAS, compared with OW age-matched adolescents without OSAS (OW control group) and normal weight (NW) control group (healthy adolescents), and to correlate spindle characteristics with obesity-related and OSAS-related parameters.

Subjects and methods

We studied 30 OW male adolescents (mean age 16.5 ± 0.3 years) and 15 NW male adolescents (mean age 16.0 ± 0.74 years). Demographic and anthropometric data were routinely collected. Body mass index (BMI) was converted to a sex- and age-specific BMI percentile using standardized norms [15].

It should be noted that sleep spindle features as well as OSAS have a sexual dimorphism [16, 17]. So, females having a higher number of spindles and higher spindle density than males, but men are especially vulnerable to sleep apnea. Since we did not aim to examine gender differences of sleep spindle activity in OW adolescents, we have included only boys as the most assailable to OSAS.

Forty-five recruited adolescents were divided into three groups in accordance with the polysomnographies (PSG) results (18 OW OSAS patients, 12 OW control patients and 15 NW control patients).

Study inclusion criteria were: BMI ≥25 kg/m^2 for OW patients and BMI = 18.5–24.9 kg/m^2 for the NW adolescents, apnea/hypopnea index (AHI) ≥5/h for OSAS patients and AHI <1.5/h for controls [18], male of 14–17 years. Adolescents were not included in the study if they had received a diagnosis of a sleep disorder (including primary snore) other than OSAS, or were already established on treatment.

Procedures were approved by the Scientific Centre for Family Health and Human Reproduction Problems (SC FHHRP) Review Board, and participants provided written informed consent.

PSG were conducted at the Sleep Center of the SC FHHRP. PSG data were collected using the GRASS-TELEFACTOR Twin PSG (Comet) with the amplifier As 40 with an integrated module for sleep SPM-1 (USA). Subjects went to sleep between 10 p.m. and 11 p.m., according to their own habitual bed times. Six EEG derivations (Fp3–A2, Fp4–A1, C3–A2, C4–A1, O1–A2, and O2–A1), two electrooculography channels, submental muscle tonus, electrocardiogram, airflow pressure by oro-nasal transducer, thermistor, snoring, thoracoabdominal respiratory movements, and blood oxygen saturation, leg movements and body position were recorded. Studies were scored according to standardized sleep stage [19]. Obstructive apneas were defined as at least a 90% reduction in the thermal signal amplitude, whereas hypopneas were defined as diminution of at least 30% of the nasal pressure signal that was associated with an arousal or desaturation of 3% [20]. Cortical arousals were scored according to the criteria of the American Sleep Disorders Association [21], and are expressed as total number of arousals per hour of total sleep time (arousal index, AI). Obstructive apneas and hypopneas were expressed as the number of apneas/hypopneas per hour of total sleep (AHI).

Sleep spindles in all NREM stage 2 sleep were scored visually using GRASS-TELEFACTOR PSG Twin 4.5.2 (USA) from C4–A1 EEG derivation after PSG analysis. The EEG signals were sampled at 200 Hz with high-pass band filtered at 0.7 Hz, and low-pass band filtered at 25 Hz. Power spectrum were automatically scored for consecutive 20-s epochs with Spectral Analysis option of GRASS-TELEFACTOR PSG Twin 4.5.2 (Hanning window, averages of five 4-s epochs; frequency resolution 0.25 Hz) and matched with the corresponding sleep stages. Spindles were defined as a waveform with frequency between 11.0 and 15.9 Hz, at least 0.5 s in length, approximately equivalent amplitude or within an approximately sinusoidal envelope and composed of waves of approximately consistent frequency and of a narrow, conical shape.

Spindle activity was operationalized as number of spindles (total number of spindles in stage 2 sleep); mean spindle density (spindles/min of stage 2 sleep); maximum spindle amplitude (μV); mean spindle duration (the average duration of the spindles in s); and mean spindle frequency (mean central frequency in Hz). Mean spindle frequency and amplitude were estimated using fully automated sleep stager (FASS) option of GRASS-

TELEFACTOR PSG Twin 4.5.2. Other spindle activity parameters were marked using a manual cursor program and visually estimated.

All statistical tests were performed using Statistica v6.0 (StatSoft, USA). For descriptive statistics, continuous variables are presented as mean ± standard deviation. One-way analysis of variance (ANOVA) was applied to assess potential differences in participants characteristics and polysomnographic data (age, BMI, AHI; min SpO_2; time with SpO_2 <90%; arousal index; total sleep time; sleep efficiency; sleep stages 1 and 2; slow wave sleep; rapid eye movement sleep) and in sleep spindle characteristics between groups (OSAS patients, OW controls and NW controls). The pairwise comparison of continuous data was conducted using the unpaired *t* tests and the non-parametric Mann–Whitney test for independent data sets. Spearman correlation was used to evaluate the relationship between spindle characteristics, BMI and OSAS-related PSG parameters. A value of $P < 0.05$ was considered statistically significant.

Results

Characteristics and PSG data for the participants were analyzed. As a result of the unpaired *t* tests, patients and controls were well-matched for age, but there were significant differences ($P < 0.05$) on body mass index between NW controls and both OW groups (NW control group versus OW control group and NW control group versus OSAS group). Mann–Whitney test showed that AHI, time with SpO_2 <90%, arousal index, sleep stages 2 were higher, and min SpO_2, sleep efficiency, slow wave sleep, rapid eye movement sleep were lower in OSAS patients compared both OW and NW controls (Table 1).

Spindle data are presented in Table 2. Mann–Whitney test showed that the number of sleep spindle density was significantly higher in OW adolescents with OSAS than in the both control groups ($P < 0.05$). However, maximum spindle amplitude and spindle frequency were significantly lower in the 1st group than in other groups ($P < 0.05$). There was no significant change in spindle duration between the three groups.

Figure 1 shows some examples of spindle detection in an OW OSAS patient, in an OW control patient and in an NW control adolescents.

Spearman rank-order correlations were conducted to determine relationships between sleep spindle characteristics both and BMI and OSAS-related PSG parameters as AHI, SaO_2 and total AI in OW OSAS adolescents (Table 3). No significant correlations were found between obesity-related parameter (BMI) and the all spindle activity measures. Of the different sleep spindle parameters, only the spindle frequency was negatively correlated with AHI

Table 1 Participants characteristics and polysomnographic data

	OW adolescents with OSAS	OW controls	NW controls	*P*
N	18	12	15	–
Age, years	16.5 ± 0.3	16.1 ± 0.2	16.0 ± 0.7	NS
Males, *N* (%)	18 (100)	12 (100)	15 (100)	–
BMI (kg/m^2)	28.2 ± 2.7	27.1 ± 1.5	19.4 ± 2.1	*<0.05*
AHI, N/h	13.7 ± 1.5	1.1 ± 0.5	1.0 ± 0.1	**<0.05**
Min SpO_2, %	89.8 ± 1.1	95.1 ± 0.5	96.0 ± 0.7	**<0.05**
Time with SpO_2 <90%, % TST	3.1 ± 1.7	0.1 ± 0.0	0.0 ± 0.0	**<0.05**
AI, N/h	28.6 ± 2.4	16.7 ± 1.3	14.1 ± 1.5	**<0.05**
TST, min	471.3 ± 50.9	468.1 ± 38.8	461.3 ± 41.1	NS
SE, %	72.1 ± 3.2	89.7 ± 2.5	91.0 ± 1.8	**<0.05**
S1, % TST	3.5 ± 1.5	2.3 ± 1.7	2.1 ± 0.8	NS
S2, % TST	71.2 ± 9.1	49.2 ± 6.7	52.5 ± 3.6	**<0.05**
SWS, % TST	12.4 ± 2.1	16.9 ± 1.5	17.2 ± 2.0	**<0.05**
REM, % TST	13.4 ± 3.1	20.7 ± 3.5	21.3 ± 2.8	**<0.05**

Data are mean ± standard deviation or *N* (%)

N number of participants, *BMI* body mass index, *AHI* apnea hypopnea index, *min* SpO_2 minimal oxyhemoglobin saturation by pulse oximetry, *AI* arousal index, *TST* total sleep time, *SE* sleep efficiency, *S1, S2* sleep stages 1 and 2, *SWS* slow wave sleep, *REM* rapid eye movement sleep, *OW* overweight, *NW* normal weight, *OSAS* obstructive sleep apnea syndrome

Significant differences between NW controls and both OW groups (NW control group versus OW control group and NW control group versus OSAS group) are indicated by italic print. Significant differences between OSAS and both control groups (OSAS group versus NW control group and OSAS group versus OW control group) are indicated by bold print

Table 2 Sleep spindle characteristics in patients with obstructive sleep apnea syndrome, overweight and normal weight participants

	OW adolescents with OSAS ($n = 18$)	OW controls ($n = 12$)	NW controls ($n = 15$)
Number of spindles, *n*	745 ± 219*	254 ± 76	311 ± 84
Spindle density, *n*/30 s epoch	4.0 ± 1.3*	1.1 ± 0.4	0.9 ± 0.1
Maximum spindle amplitude, μV	19.8 ± 0.6*	29.5 ± 0.5	31.2 ± 0.8
Spindle duration, s	1.1 ± 0.6	1.06 ± 0.3	1.02 ± 0.4
Spindle frequency, Hz	11.2 ± 0.3*	13.7 ± 0.4	14.1 ± 0.2

Data are mean ± standard deviation

OW overweight, *NW* normal weight, *OSAS* obstructive sleep apnea syndrome

* Significant difference between OSAS and both control groups (OSAS group versus NW control group and OSAS group versus OW control group), $P < 0.05$

($r = -0.63$; $P = 0.02$), min SaO_2 ($r = -0.67$; $P = 0.01$) and AI ($r = -0.57$; $P = 0.03$). Spindle density, spindle duration and maximum spindle amplitude did not correlate significantly with these OSAS-related parameters.

Discussion

This is the first study to evaluate sleep spindle activity during sleep in OW adolescents with OSAS. Nevertheless, adolescence is a transitional stage from childhood to adulthood and is associated with many changes in sleep [22]. This includes the need for study of adolescents as a separate group. In the current study, there was a significant change in the sleep spindle characteristics in OW adolescents with OSAS. Specifically, number of spindles and spindle density were significantly higher, but maximum spindle amplitude and spindle frequency were significantly lower in OSAS patients, as compared in both OW controls and NW controls. So, the study Himanen and colleagues [23] also demonstrates marked differences in spindle frequency patterns between OSAS patients and normal controls. In our group of OW subjects with OSAS we did find significant correlations between spindle frequency and classic OSAS-related sleep parameters (AHI, min SaO_2 and total AI), but no significant correlations were found between spindles and BMI. This is in controversial with findings that the sleep disruption in OSAS adults, which is caused by apneas and hypopneas, is only poorly reflected on conventional sleep parameters [24, 25]. We assume that the finding of increase of the number of spindles and spindle density in adolescents with OSAS may be a specific manifestation of initial brain adaptation to intermittent hypoxia and thalamocortical neural activation; whereas, in middle-aged adults poor changes of sleep spindle activity may be associated with sustainable adaptation to chronic decrease brain perfusion.

It has been shown that the frequency of individual sleep spindles increases across NREM sleep episodes. Numerous sleep-EEG studies have identified two different types of sleep spindles: fast and slow [26]. The fast spindles, ranging from 12.5 to 15 Hz, appear predominantly at the initiation and termination of NREM sleep, while the slow spindles, ranging from 11 to 13.5 Hz, appear during deeper NREM sleep [27]. In the study of Tagaya and co-workers, healthy young males showed higher frequency ranges during initiation and termination of NREM sleep, whereas further evolution and devolution of NREM sleep was represented by lower frequency ranges [28].

It is known, that spindle waves are generated in the thalamus and spindle activity is thus a stable and reliable marker of sleep disturbances [29]. Phasic inhibition of thalamocortical relay neurons may additionally block sensory transmission to the cortex during sleep with apnea episodes [30]. So, we can assume that increased ability to arousal in response to excessive respiratory stimuli in OSAS patients causes frequent appearance of spindles as a putative mechanism to protect the sleeping brain from arousing stimuli, and thereby enhancing sleep consolidation. In OSAS patients the spindles were already slower in the beginning of the first NREM sleep episode and remained slower throughout the night [23]. There was no pediatric studies in which evaluated the features of the fast and slow spindles in OW OSAS adolescents. In our work, we did not study separated two types of sleep spindles, but this will be interesting for the future studies.

In conclusion, sleep spindle characteristics are related to OSAS presence, but not to the weight excess. Since sleep spindle pattern differences between groups were apparent, we suggested that the slow and low-amplitude spindles in the OSAS group might indicate long hyperpolarization rebound sequences with low hyperpolarization level, possibly indicating altered neural mechanisms in the structures regulating spindle activity in OSAS. Probably, the increased spindle number and spindle density in adolescents with OSAS are physiological evidence of the adaptive cortical response to sleep fragmentation and hypoxia because of multiple brief occlusions or loads applied during inspiration in impaired sleep, an adaptive response to sleep fragmentation and hypoxia. Future studies evaluating

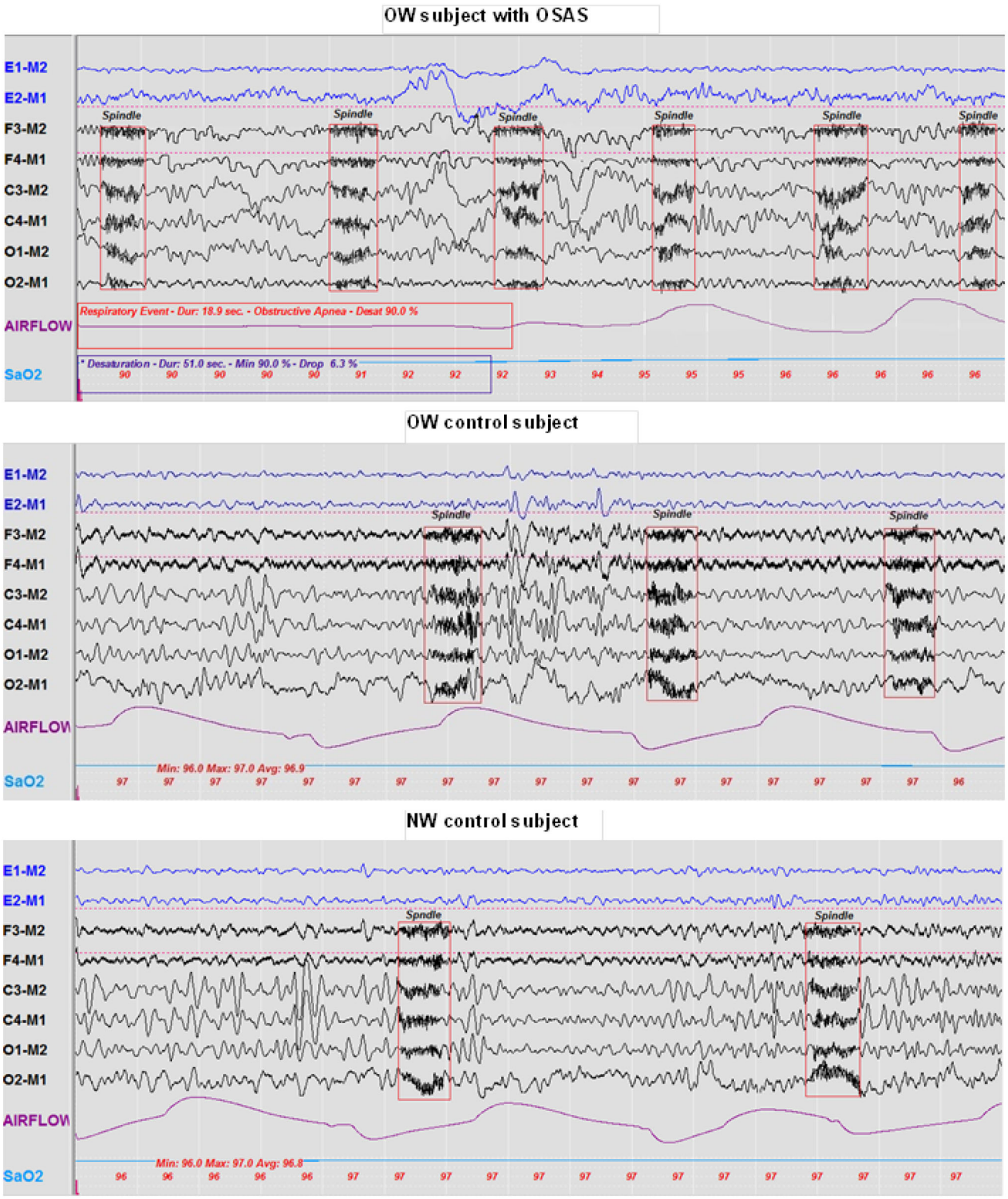

Fig. 1 Examples of visual spindle detection in an OW patient with OSAS (*top tracing*), in an OW control patient (*middle tracing*) and an NW normal control (*bottom tracing*), 20-s epoch. High spindle density in an OW OSAS boy is associated with respiratory event (obstructive apnea) and desaturation

Table 3 Correlations between S2 sleep spindle characteristics with BMI and OSAS-related polysomnographic parameters in overweight patients with obstructive sleep apnea syndrome

	BMI	AHI	Min SpO_2	AI
Number of spindles, *n*	0.18	0.09	0.19	0.07
Spindle density, *n*/30 s epoch	0.31	0.01	0.15	0.13
Maximum spindle amplitude, μV	0.37	0.23	0.05	0.25
Spindle duration, s	−0.24	−0.13	0.03	0.31
Spindle frequency, Hz	0.14	**−0.63**	**−0.67**	**−0.57**

S2 sleep stage 2 of NREM (non-rapid eye movement sleep), *OSAS* obstructive sleep apnea syndrome, *BMI* body mass index, *AHI* apnea hypopnea index, *min* SpO_2 minimal oxyhemoglobin saturation by pulse oximetry, *AI* arousal index. Bold values are significant at $P < 0.05$

sleep spindle characteristics after effective non-invasive continuous positive airway pressure (CPAP) treatment of OSAS in OW adolescents will be needed.

Author contributions IM substantial contributed to the conception, design and analysis of data for this work, finally approved of the version to be published, and agreed to be accountable for all aspects of the revised work in ensuring that questions related to the accuracy or integrity of any part of the revised work are appropriately investigated and resolved. OB substantial contributed to the acquisition, analysis, and interpretation of data for this work, drafting the work, and agreed to be accountable for all aspects of the revised work in ensuring that questions related to the accuracy or integrity of any part of the revised work are appropriately investigated and resolved. LR substantial contributed to the conception of this work, revising it critically for important intellectual content, and agreed to be accountable for all aspects of the revised work in ensuring that questions related to the accuracy or integrity of any part of the revised work are appropriately investigated and resolved. OB revised the manuscript critically after the first reviewing, finally approved of the version to be published, and agreed to be accountable for all aspects of the revised work in ensuring that questions related to the accuracy or integrity of any part of the revised work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest All authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Research involving human participants and/or animals All procedures performed in this study involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments. This study has been approved by the Scientific Centre for Family Health and Human Reproduction Problems Review Board.

Informed consent Informed consent was obtained from all individual participants included in the study.

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