BREATHING DURING SLEEP; STUDIES RELATED TO UPPER AIRWAY CALIBRE IN PREGNANCY

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Declaration

I declare that I was the principal investigator in all of the studies conducted within this thesis and that the contents of this thesis are my own work. Assistance with these studies was provided by other staff members of the Department of Sleep Medicine, as outlined in the acknowledgements.

The studies reported in this thesis were conducted between August 2001 and the October 2004. They were conducted in the Edinburgh sleep centre or, the Simpson Memorial Maternity Pavilion in the Old Royal Infirmary, and the Department of Sleep Medicine, or Simpson Centre for Reproductive Health of the Royal Infirmary of Edinburgh in the New Royal Infirmary.

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Abstract

Snoring is common in pregnancy, and has been associated with an increased incidence of both maternal hypertension and preeclampsia, as well as an increased incidence of low birth weight infants and significantly poorer Apgar scores at birth. Patients with pre-eclampsia have episodes of partial upper airway (UA) obstruction during sleep. These repeated episodes are associated with further increases in blood pressure (BP). Preliminary evidence indicates that preventing episodes of airflow obstruction with continuous positive airway pressure (CPAP) therapy may reduce BP in pre-eclampsia. Snoring and apnoea-hypopnoea index (AHI) subside within a few months of delivery. However, there have been no studies measuring the effect of pregnancy or the postpartum period on UA dimension. The present study aimed to compare UA dimensions in pregnant and nonpregnant women and in patients with pre-eclampsia with a follow-up of the pregnant women post partum. Apart from snoring, excessive daytime sleepiness (EDS) is the most common complaint among pregnant women. A majority of the pregnant women including preeclamptic women have experienced EDS during pregnancy, but it is not clear whether EDS is associated with snoring. Thus, this thesis also examines whether snoring and sleepiness are linked in pregnancy and pre-eclampsia.

In a cross-sectional study with a 3 way comparison, 50 pregnant, 37 pregnant women with pre-eclampsia in the third trimester of pregnancy, and 50 nonpregnant women were consecutively recruited. Control subjects were matched with pregnant women (both healthy pregnant and pre-eclamptic women) for age and pre-pregnancy BMI. UA dimensions were measured using acoustic reflection. Habitual snoring was reported by 15% of nonpregnant women, 28% of pregnant women, and 48% of pre-eclamptic

women ($p < 0.001$). Pre-eclamptic women had narrower UAs compared to non-pregnant or healthy pregnant women in seated position ($p < 0.02$). Supine oropharyngeal junction area was also less in the women with pre-eclampsia than in the nonpregnant women ($p = 0.01$) but similar in women with pre-eclampsia and pregnant women ($p > 0.3$). When seated, pregnant women had wider UAs than nonpregnant women ($p < 0.02$). There was a non-significant trend for pregnant women to have narrower airways than non-pregnant women when supine. The data suggest that there may be pregnancy related changes in UA dimension, but this was not clear from this cross-sectional study of 3 groups, non-pregnant, pregnant and pre-eclamptic women.

In a cross sectional study (with a 2 way comparison) with follow up of the pregnant women at least three months after their delivery, 100 women in the third trimester of pregnancy and 100 nonpregnant women, matched for age and BMI, were recruited. Fifty women agreed to be restudied 3 months after delivery. UA dimensions were measured using acoustic reflection. Snoring was less common in nonpregnant (17%) than pregnant women (41%) and returned to nonpregnant levels after delivery (18%). Pregnant women had significantly smaller UAs than nonpregnant women at the oropharyngeal junction when seated and smaller mean pharyngeal areas in the seated, supine and lateral postures compared with the nonpregnant females ($p< 0.05$). Pregnant women had smaller mean pharyngeal areas compared with post-partum in the seated, supine and lateral postures ($p< 0.03$). This study confirmed increased snoring and showed narrower UAs during the third trimester of pregnancy.

One-hundred sixty-seven healthy and 82 pre-eclamptic women in the third trimester of pregnancy and 160 non-pregnant women completed a sleep questionnaire in a

prospective questionnaire-based study. Age and height did not differ significantly between groups ($P>0.2$), but pre-eclamptic women were heavier than pregnant and non-pregnant women and had higher BMI than pregnant women before pregnancy (all $P<0.05$). Seventeen percent of control, 35% of pregnant and 59% of pre-eclamptic women snored ($P<0.001$), but pre-pregnancy snoring rates (both 10%) were similar to those in non-pregnant women (17%) ($p>0.1$). Sleepiness was reported by 12% of non-pregnant, 23% of pregnant and 15% of pre-eclamptic women ($p<0.04$), but non-pregnant women had lower mean Epworth Sleepiness scores than both pregnant and pre-eclamptic groups ($P<0.001$). Snoring was correlated with ($p=0.002$), but explained only <2% of the variance in sleepiness.

The studies presented in this thesis indicate that UA narrowing occurs in the third trimester of pregnancy, probably due to pregnancy-related changes. It is likely that reduced UA calibre may contribute to the increased rate of snoring, breathing pauses and sleepiness in the third trimester of pregnancy, especially in patients with pre-eclampsia. However, sleepiness in pregnancy is largely due to factors other than snoring or breathing pauses.

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List of Abbreviations and Definition of Terms

AASM – American Academy of Sleep Medicine

ABPM – Ambulatory blood pressure monitoring

AHI – Apnoea/hypopnoea index = apnoeas + hpopnoeas/hour slept

Av – Average

BMI – Body mass index

BP – Blood Pressure

CHF – Congestive heart failure

CO – Cardiac output

CI – Confidence interval (e.g., 95% CI)

COPD – Chronic obstructive pulmonary disease

CPAP – Continuous positive airway pressure

nCPAP– Nasal continuous positive airway pressure

CSA – Cross sectional area

CT – Computerised tomography

CV – Coefficient of variation

CVS – Cardiovascular system

DBP – Diastolic Blood Pressure

DeO_2 – Oxygen desaturation

DOS – Date of Study

DOB – Date of Birth

EDD – Expected Delivery Date

ECG – Electrocardiogram

EDS – Excessive daytime somnolence

EEG – Electroencephalography

EMG – Electromyography

EOG – Electrooculography

ESS – Epworth sleepiness score

FRC – Functional Residual Capacity

GG – Genioglossus

Hr(s) – Hour(s)

ICC– Intraclass correlations coefficient

ICSD – International Classification of Sleep Disorders

IFLI – Inspiratory flow limitation index

IQR – Interquartile range

IUGR – Intrauterine growth retardation

LAUP – Laser assisted uvulopalatoplasty

MAD – Mandibular advancing device

Map – Mean arterial pressure

Min – Minutes

mmHg – millimeters of mercury

MRI – Magnetic resonance imaging

MRS – Mandibular repositioning splint

MSLT – Multiple sleep latency test

NC – Neck Circumference

No – Subject number

NOB – Number of Baby

NREM – Non-rapid eye movement sleep

OA – Oral appliance

OPJ – Oropharyngeal junction

IQR – inter-quartile range

OSAHS – Obstructive sleep apnoea/hypopnoea syndrome

PaO_2 – Arterial oxygen tension

PaCO2 – Arterial carbon dioxide tension

PO2 – Partial pressure of oxygen

PCO2 – Partial pressure of carbon dioxide

Pes – Esophageal pressure

PIH – Pregnancy-induced hypertension

PSG – Polysomnography

RDI – Respiratory disturbance index

RERAs – respiratory-related arousals

REM – Rapid eye movement

ROS – Reactive oxygen species

SaO_2 – Oxygen saturation

SBP – Systolic blood pressure

SD – Standard deviation

SE – Sleep efficiency

Secs – Seconds

SEM/SE – Standard Error of the Mean

SIDS – Sudden infant death syndrome

SHHS – Sleep Heart Health Study

SIGN – Scottish Intercollegiate Guidelines Network

SOL – Sleep onset latency

SPT – Sleep period time

SWS– Slow wave Sleep

TNF-α – Tumor necrosis factor-a

TP – Tensor Palatini

TST – Total sleep time

UARS – Upper Airway Resistance Syndrome

UPPP – Uvulopalatopharyngoplasty

Vp – pharyngeal volume

Vs – Versus

Waist-hip ratio – WHR

Yr(s) – Year(s)

CHAPTER 1
AN OVERVIEW OF SLEEP DISORDERED BREATHING

1.1 Introduction

The clinical significance of sleep disordered breathing was recognized 35 years ago. Sleep-disordered breathing refers to the entire spectrum of breathing disorders during sleep, including central apnoea and hypoventilation (Lugaresi et al 1983). Although obstructive Sleep Apnoea/Hypopnoea syndrome (OSAHS) and sleep-disordered breathing seem to describe overlapping phenomena, OSAHS may be considered a subset of sleep-disordered breathing. Pathological states of sleep-disordered breathing range from simple snoring to upper airway resistance syndrome (UARS) to OSAHS to the obesity hypoventilation syndrome (Lugaresi et al 1983). Sleep-disordered breathing is a major public health concern, as it is associated with, or a cause of, serious chronic illness, including systemic hypertension and congestive heart failure, and increased mortality rates. There is also growing evidence showing that pregnancy and pre-eclampsia may be linked with this disorder.

This first chapter presents general background of sleep-disordered breathing including a historical review, definitions, epidemiology, predisposing factors, diagnosis, clinical presentations, complications, associations and treatments.

1.2 Historical review

Although the awareness of this condition is relatively new, early description of sleep-disordered breathing goes back as far as literary antiquity. One of the earliest accounts is from classical Greek literature and concerns Dionysius, tyrant of Heraclea in the 4th century BC. This grossly obese man suffered from fear of suffocation. In order to

stimulate his breathing, long thin needles were thrust into his abdomen. These observations suggest an association between obesity and sleep-disordered breathing (Kryger 1983).

The most well-known historical description of snoring and sleepiness is Charles Dickens' portrayal of Joe, the fat boy in *The Posthumous Papers of the Pickwick Club* (Dickens 1837). The fat boy Joe was described as snoring loudly and being extraordinarily sleepy, both of which are qualities accepted as hallmarks of severe obstructive sleep apnoea today. Both Osler in 1918 (Osler, Sir William *The Principles and Practice of Medicine* as cited by Guilleminault et al 1976) and Burwell et al in 1956 (1956) were inspired by Dicken's character Joe, the fat boy. When describing a particular type of obese patient with hypoventilation and hypersomnolence during daytime, they coined the term "Pickwickian Syndrome". However daytime somnolence, nocturnal electroencephalography (EEG) arousal and sleep architecture were not associated until a decade after Burwell's article was published. Gastaut in France and Jung in Germany independently reported the recognition that apnoeas caused sleepiness (Jung and Kuhlo 1965, Gastaut et al 1966) recording simultaneous EEG and respiratory signals in Pickwickian patients. They emphasised that "the majority of individuals suffering from the Pickwickian Syndrome drowse during the day and sleep badly at night because of a primary disturbances in the wakefulness-sleep regulation which as such is based on their obesity" (Gastaut et al 1966). In 1965 Jung and Kuhlo presented a detailed list of features of sleep apnoea, explaining that sleepy obese patients with the Pickwickian Syndrome have the recurrent breathing pauses associated with sleep disruption, oxyhaemoglobin desaturations, and cardiac arrhythmias (Jung and Kuhlo 1965).

Since Gastuat and Jung's reports, the field of sleep medicine has advanced rapidly and provoked interest in investigating respiratory changes during sleep. The first symposium on sleep-related respiratory problems was organised by Lugaresi and Sadoul in Italy in 1972 (Guilleminault et al 1976). This symposium was a landmark meeting due to the fact that it drew together neurological and pulmonary physicians interested in sleep. In this conference, sleep apnoea syndrome was defined and named "the sleep-induced apnoea syndrome". Guilleminault played an important role in sleep medicine, reviewing sleep-disordered breathing and linking it with cardio-pulmonary disorders in 1976 (Guilleminault et al 1976). This review classified the various forms and described the symptoms of the disease of the obstructive sleep apnoea/hypopnoea syndrome including snoring and excessive daytime sleepiness (EDS).

In 1981 Dr. Colin Sullivan introduced a new treatment which eliminated the problem of the collapse of the upper airway (UA) by using continuous positive airway pressure (CPAP). This therapy became the treatment of choice for patients with sleep-disordered breathing, providing rapid improvement of symptoms in sleep medicine (Sullivan et al 1981).

1.3 sleep-disordered breathing as a spectrum of breathing disorders during sleep

As mentioned earlier, the term sleep-disordered breathing has been used synonymously with the OSAHS. In a broader sense, however, the disorders associated with breathing abnormalities during sleep exist along a spectrum of severity. The physiologic spectrum of sleep-disordered breathing may be mapped as moving from partial airway collapse to increased upper-airway resistance (which is experienced as loud snoring and episodes of

hypopnoea), to complete airway collapse (experienced as breathing pauses lasting up to 60 seconds or more) (Young et al 1993). The mildest form of sleep-disordered breathing is intermittent snoring without episodes of apnoea or hypoventilation, and the most severe form of sleep-disordered breathing is arguably the obesity-hypoventilation syndrome (Lugaresi et al 1983). In between these two endpoints are disorders of gradually-increasing impact on morbidity and mortality: habitual snoring, UARS, and OSAHS. In this thesis these forms are discussed separately for simplicity, but these particular conditions are probably a continuum of problems all of which have the same pathophysiology.

1.4 Definitions of the forms of sleep-disordered breathing

1.4.1 Snoring

Primary snoring is defined as loud inspiratory sounds in sleep without apnoea or hypoventilation (American Academy of Sleep Medicine 2001), which occurs due to turbulent air flow through a narrow oropharyngeal or nasopharyngeal space (Bradley et al 1986). Habitual snoring is a chronic condition which may be described as snoring "almost every night", or "every night per week" (Young et al 1993, Young et al 2001). All snorers have partial UA obstruction and most habitual snorers have complete episodes of UA obstruction during sleep (Guilleminault et al 1976, American Academy of Sleep Medicine 2001).

Snoring has been found to be an independent risk factor for the development of hypertension (Lindberg et al 1998a). Studies have also shown links between snoring, and pre-eclampsia and foetal growth restriction (Franklin et al 2000, Guilleminault et al 2000). Moreover, snoring is associated with daytime sleepiness due to sleep

fragmentation (Lindberg et al 1998b, Young et al 1993, Martin et al 1996). One of the problems with snoring is that it is a clinical sign the presence of which is often ascertained by questioning the individual. Thus there is a significant amount of variability in the accuracy of reporting depending on the presence or absence of a sleeping partner, that partner's threshold for identifying and reporting back nocturnal noises as snoring and the individual snorer's threshold for indicating they snore. There are very few studies in which snoring has been objectively defined and recorded and even here techniques and definitions vary.

1.4.2 Obstructive Sleep Apnoea / Hypopnoea Syndrome –OSAHS

OSAHS, a severe form of sleep-disordered breathing, is characterised by recurrent episodes of complete (apnoea) or partial UA obstruction (hypopnoea) at the pharyngeal level during sleep, resulting in cortical arousal and oxygen desaturation (Guilleminault et al 1976, American Academy of Sleep Medicine 2001), with sleep disturbance and transient rises in blood pressure (BP) (Davies et al 2000).

Apnoeas were defined by Gastaut et al (1966) as episodes of complete cessation of respiratory airflow lasting at least for 10 seconds and classified as either obstructive, or central or mixed; this classification was made on the basis of the presence or absence of respiratory effort. The term obstructive apnoea is described as a cessation of airflow due to UA obstruction but with continued respiratory effort. A central apnoea is defined as the cessation of airflow with the absence of respiratory effort due to a disorder of the brainstem (secondary to age, cardiac, and cerebrovascular disease). This can only safely be determined by the absence of oesophageal pressure swings or respiratory muscle activity on electromyography (EMG). Definitions based on the absence of

thoracoabdominal movement lead to the inclusion of obstructive events in the very obese and probably also CPAP responsive "central" apnoeas which can be due to reflex inhibition of inspiratory effort following UA occlusion. A mixed apnoea (complex apnoea) is a combination of both central and obstructive components. It is defined by the cessation of airflow and an absence of respiratory effort early in the episode, followed by resumption of respiratory effort in the latter part of the episode (Gastaut et al 1966). Although the definition of apnoea is highly uniform, there is no consensus on the definitions of an apnoea's subgroups due to differences in measurement techniques.

The term apnoea index which is described as the number of apnoeas per hour of sleep was developed after the notion of an apnoea had been defined. Obstructive sleep apnoea syndrome was first defined by Guilleminault et al (1976) as the criterion of 5 or more apnoeas per hour.

The new terms were produced with the recognition of hypopnoea and arousal in later years. The clinical importance of hypopnoea was first recognised in Edinburgh by Gould et al (1988). Hypopnoea was defined as a 50% reduction in thoraco-abdominal movement compared to the baseline value of immediately preceding breaths lasting more than 10 seconds. Although American Academy of Sleep Medicine Task Force (1999), in a consensus statement, provided some criteria for the definition of hypopnoea, the required criteria e.g. a desaturation of ≥3% and recording techniques are still controversial. However, the importance of hypopnoea is genuinely accepted and the apnoea plus hypopnoea index per hour of sleep (AHI) is usually computed to diagnose this syndrome. As a result of these events, today the term, OSAHS, is used as a common name.

The term, respiratory disturbance index (RDI), has been used to report the number of respiratory events including arousals in addition to apnoea and hypopnoea per hour slept (Hosselet et al 2001). An arousal is defined by a return of alpha or theta rhythm in the EEG of ≥1.5 seconds and a rise in EMG activity during this period (Atlas Task Force of the American Sleep Disorders Association 1992, Mathur and Douglas 1995a).

The best feasible diagnostic criteria is based on both symptoms and AHI which include AHI≥5 determined by overnight monitoring with full polysomnography (PSG), unexplained excessive daytime sleepiness or a combination of at least 2 other major symptoms (American Academy of Sleep Medicine Task Force 1999, Young et al 2002a).

There is no universal agreement on the severity of the disease although the severity can be determined in terms both of AHI and symptoms. Defining clinically-significant sleep apnoea is arbitrary due to the fact that there is a continuum of potential AHIs, which ranges from trivial to severe (Lugaresi et al 1983). Different centres also use different techniques such as full PSG or limited sleep studies etc. and different criteria such as the apnoea index, AHI and RDI with or without oxygen desaturation to define the severity of the OSAHS. However, an AHI of 15 or greater is considered a clinically important cut-off point, but this index is only one marker of OSAHS as symptoms must occur for the syndrome to exist. Any stratification of the severity of OSAHS in terms of health consequences requires other important parameters. Therefore, the severity of symptoms, such as sleepiness, which causes impairment of social or occupational functioning, as well as AHI needs to be considered when the severity of the disease itself is determined.

Lugaresi et al (1983) recommended a diagnostic assessment to establish the severity of the disease including both symptoms and nocturnal respiratory events. This was based on the monitoring of respiratory events during sleep and of the propensity for daytime sleepiness (using multiple sleep latency test – MSLT).

This assessment categorized the disease's severity into four subgroups.

Preclinical stage: characterized by sporadic obstructive apnoeas and O2 desaturations.

Initial stage: characterized by obstructive apnoeas, persisting during stage 1-2 and REM sleep, which are correlated with phasic desaturations.

Overt stage: characterized by obstructive apnoeas persisting for all stages of sleep with phasic desaturation which is associated with persistent falls of SaO2.

Complicated stage: characterized by alveolar hypoventilation persisting during wakefulness and phasic desaturation which is linked with persistent falls of SaO2.

Sleepiness also was categorised into four subgroups according to its severity, but these were not compatible with nocturnal respiratory events. Today these criteria are not in use, but this was one of the first such systems that emphasize the importance of symptoms to determine the severity and the significance of less severe forms of OSAHS.

In 1999 the American Academy of Sleep Medicine Task Force, for the purposes of standardising research methodology, divided OSAHS into subgroups according both to the severity of obstructive breathing events (AHI) and the severity of sleepiness.

The classification for obstructive breathing events was:

Mild: AHI of 5 to 14

Moderate: AHI of 15 to 30

Severe: AHI greater than 30

The classification for the severity of sleepiness was:

"(1) Mild: unwanted sleepiness or involuntary sleep episodes occur during activities that require little attention. (2) Moderate: unwanted sleepiness or involuntary sleep episodes occur during activities that require some attention. (3) Severe: unwanted sleepiness or involuntary sleep episodes occur during activities that require active attention."

These two systems highlight the importance of the severity of symptoms as well as nocturnal respiratory events. Clinical severity depends on the severity of the symptoms. Although severe breathing abnormalities generally cause more severe symptoms than mild-to-moderate breathing abnormalities, in some cases the severity of the symptoms does not correspond to the degree of breathing abnormality. For example a patient with severe breathing abnormalities but not being sleepy is considered less severe than a patient with both moderate breathing abnormalities and sleepy. These asymptomatic individuals do not benefit from the treatment with CPAP (Barbe et al 2001).

Any classification of severity may require modification with increasing age since AHI may increase with age (Young et al 1993, Ohayon et al 1997, Duran et al 2001). Further prospective studies are needed to confirm this.

1.4.3 Upper Airway Resistance Syndrome

A form of the spectrum of sleep-disordered breathing has been termed UARS which is used to describe generally non-obese patients with clinical features not matching those reported with OSAHS. UARS is characterized by recurrent episodes of increased airway resistance during sleep in the absence of UA collapse, hypoventilation or oxygen

desaturation (Guilleminault et al 1993). The increased respiratory effort terminated by transient alpha EEG arousals results in multiple sleep fragmentations and eventually excessive daytime sleepiness, which is confirmed by MSLT (Guilleminault et al 1993, Guilleminault and Chowdhuri 2000, American Academy of Sleep Medicine 2001). Snoring may not be a feature of UARS. The resistance to airflow is typically subtle, but leads to an increase in negative intrathoracic pressure during inspiration which can be measured using an esophageal manometer attached to a polysomnogram.

There has been dispute whether this syndrome is a distinct condition or a reflection of excessively low sensitivity in the methods used to detect hypopnoeas (Douglas 2000, Guilleminault and Chowdhuri 2000, Lindberg and Gislason 2000). There is a growing consensus that it is not a distinct condition (American Academy of Sleep Medicine 1999, Douglas 2000). In the Revised Diagnostic and Coding Manual of International Classification of Sleep Disorders (ICSD) (American Academy of Sleep Medicine 2001), UARS has not been recognized as a distinct condition by American Academy of Sleep Medicine. Additionally, respiratory-related arousals (RERAs), which are the result of increases in upper-airway resistance and resultant rises in inspiratory effort without evidence of apnoeas, hypopnoeas (Stradling and Davies 2004), are considered as a part of OSAHS by American Academy of Sleep Medicine Task Force (1999).

1.5 Epidemiology of sleep-disordered breathing

The estimation of the prevalence of this disorder is problematic because of discrepancies in (Young et al 1993, Stradling et al 1991, Young et al 2002a, Stradling and Davies 2004):

- the designs of the epidemiologic studies (from survey to a two-stage sampling procedure: subsets of participants who have suspected sleep-disordered breathing are identified by surveys/interview and then undergo a sleep study)
- the definition of the disease
- methods used for diagnosis (ranging from full PSG to simple oximetry)
- the population of the studies (from normal individuals to patients with obesity and hypertension)
- the definitions of sleepiness used

Therefore findings of various studies on prevalence estimates are extremely vulnerable to problems related to methodology.

1.5.1 Prevalence of habitual snoring

Snoring is a common problem among men (and women). The prevalence of snoring and OSAHS increases with age, and this proportion peaks between the ages of 50 to 60 years (Young et al 1993, Ohayon et al 1997). Women tend to start to snore during pregnancy and again later in life (Loube et al 1996, Franklin et al 2000, Edwards et al 2002), with an increased prevalence after menopause (Bixler et al 2001).

In an epidemiologic study of snoring and obstructive sleep apnoea in a Danish population, Jennum and Sjol (1992) showed that habitual snoring was 19.1% in males and 7.9% in females. In a two-stage cross-sectional study of 602 employees between 30 and 60 years of age, 52% of women and 64% of men reported habitual snoring and 81% of these women and 66% of these men had AHI<5 respectively (Young et al 1993).

Bearpark et al (1995) used home monitoring to measure snoring and sleep apnoea in 294 men aged 40 to 65 yr and found that 81% snored for more than 10% of the night and 22% for more than half the night.

Duran and coworkers (2001) found that habitual snoring occurred in 46% of men and 25% of women, with a significant trend to increase with age, among 2,148 subjects aged 30 to 70 years in a two-phase cross-sectional study in Spain. In the UK, a population-based telephone interview of 2,894 women and 2,078 men aged 15-100 years reported that 47.7% of males and 33.6% of females snored. This percentage increased to 97% in a patient group with suspected sleep apnoea (Whyte et al 1989).

In most studies, habitual snoring is detected according to self-reported answers, but some individuals may not be aware of, or may deny, their snoring. Thus, reliable reporting of snoring needs to be objectively recorded.

1.5.2 Prevalence of obstructive sleep apnoea/hypopnoea syndrome

There is a high variation of prevalence of OSAHS in epidemiological studies due to differing criteria as mentioned above. In 1983, one of the first epidemiologic studies was performed by Lavie (1983) in a detailed study of 78 industrial workers by PSG from an original sample of 1,502 subjects. He reported a prevalence of 1.4% for sleep apnoea (apnoea index ≥5 and EDS). However, the prevalence of OSAHS could be higher than this value, as hypopnoeas were not scored. It can not be generalised to a population due to the unique feature of the study sample (industrial workers).

In a study based on oximetry recordings in 900 males in the UK, Stradling and Crosby (1991) found that 5% of these subjects (n=46) had 4% SaO_2 desaturation greater than five per hour of sleep and symptoms of the OSAHS. Three of them had clinically severe symptomatic sleep apnoea, while 18 had sleep apnoea only in the supine position. These figures give a prevalence of 0.3% for severe symptomatic sleep apnoea and 2% for supine-related sleep apnoea. However, oximetry alone may underestimate the true number of respiratory events in a night (Douglas et al 1992). Thus, this study may underestimate the prevalence of OSAHS in this population.

Jennum and Sjol (1992) determined nocturnal respiration in 748 participants aged 30-60 using inductive plethysmography. 10.9% of males and 6.3% of females had RDI ≥ 5. The prevalence of OSAHS (RDI ≥ 5 and EDS) was 0.9% in females, 1.9% in males, and in total 1.4% of both males and females.

Young et al (1993) estimated that 9.1% of females and 24% of males had an AHI ≥ 5 in a random sample of 602 employed men and women aged 30-60 years. When the minimal diagnostic criteria for the OSAHS (an AHI ≥ 5 and EDS) were taken into account, prevalence figures were 2% for females and 4% for males in a similarly-aged population. This is confirmed by Bearpark et al (1995) who reported that 26% of 294 men had a RDI ≥5 and 10% had a RDI≥10, and the prevalence was 3% for the OSAHS in men, using an RDI ≥ 5 and EDS.

In a population-based telephone interview in the UK, OSAHS was thought to be present in 3.5% of males and 1.5% of females. However, subjective reporting of

symptoms on the phone is not an accurate method of determining the true incidence and severity of sleep-disordered breathing (Ohayon et al 1997).

More convincing data on the prevalence of OSAHS come from four large prevalence studies which used similar criteria. These criteria include an AHI of 5 per hour plus symptoms, similar methods and two-stage sampling procedure (survey/interview and then PSG). Thus these studies reported broadly comparable results (Young et al 1993, Bixler et al 1998, Bixler et al 2001, Duran et al 2001). On the basis of these studies, Young et al (2002a) estimated that 20 % of white men and women with mean BMIs of 25 to 28 kg/m^2 have at least mild OSAHS and 7% of them have at least moderate OSAHS. In the UK, Stradling and Davies 2004, on the basis of their previous work, estimated that the prevalence was approximately 0.5% amongst men (mean age 48.2 years) with a mean BMI of 24.9 kg/m^2 and roughly 1.5% in a similar population (mean age 52 years), with a mean BMI of 27.1 kg/m^2. This estimation was made according to a strict definition, which took into consideration those subjects with moderate to severe disease, who had clear sleepiness.

Two-stage procedures, which give comparable results, can lead to a serious underestimation of prevalence when they are based on an extremely conservative set of assumptions (Lindberg and Gislason 2000, Young et al 2002a). Prevalence of undiagnosed OSAHS in these studies ranged from 0.3 to 5% (Young et al 2002a).

In summary, undiagnosed sleep-disordered breathing is relatively common and has a wide range of severity in middle-aged women and men. There is a need for thorough estimation of prevalence of OSAHS for better recognition and treatment of severe,

symptomatic OSAHS due to its associations with cardiovascular and behavioural morbidity and mortality.

1.5.3 Prevalence of upper airway resistance syndrome

Little is known of the prevalence of UARS since population-based studies of it are lacking, which is not surprising as the presence of the condition is not clearly established. A retrospective case–control study of 334 women, aged 18 years and older showed that 11.4 % of women were reported to have UARS (Guilleminault et al 1995). In this study, nose and mouth thermistors plus desaturation were used to define hypopnoeas. Thermistors are not sensitive to detect hypopneas, and slim, young individuals do not desaturate with brief apnoeas or hypopnoeas. Thus, hypopnoeas could have been missed. Also an Epworth sleepiness score (ESS) ≥ 9 has been used to identify sleepiness while in general a person with minimum ESS ≥ 11 is accepted to be sleepy. Therefore the percentage of UARS might be overestimated. Chervin and Aldrich (1997) reported a much higher (21%) incidence of UARS using esophageal pressure (pes) monitoring during PSG in 155 patients aged 3-83 yr. This wide age range may likely increase the percentage of UARS in this population; in particular children with narrow UAs may be more likely to suffer from UARS. They notified that patients with UARS who had AHI<10 per hour had sequences of increasing respiratory effort that repeatedly led to sleep disruption or intrathoracic pressures that were more negative than -20 cm H2O. Polo-Kantola et al (2003) showed that 17.7% of healthy postmenopausal women without symptoms suggestive of OSAHS had partial UA obstruction, manifesting as an increased respiratory resistance pattern in a static-charge-sensitive bed. This method measures effort, but it does not measure airflow nor does it determine whether this increased respiratory resistance is associated with episodes of

obstructive respiratory events and flow limitation. Therefore this percentage may be overestimated.

Rees and co-workers (2000) in Edinburgh compared the frequency and significance of increased upper-airway resistance and arousal between eight symptomatic patients with UARS (ESS >10, AHI <15) and a matched healthy control group. They found that episodes of flow limitation or resistive events were equally frequent in both groups. However, at the end of an episode, the patients had more negative pleural pressure (-15 and -11 cm H2O) and more cortical arousals (10 and 3 per hour slept) than the control subjects. The authors suggested that "the clinical significance of resistive events needs to be interpreted with caution in order to avoid over diagnosis of the UARS".

1.6 The incidence and progression of sleep disordered breathing

Recent longitudinal studies which have examined the incidence of sleep-disordered breathing in the same population on more than one occasion over a given period of time suggest that AHI significantly increases with snoring, obesity and advanced age. One large study of the natural history of sleep-disordered breathing in a group of 690 (from 948 subjects) middle-aged men and women who were evaluated twice at 4-year intervals reported that weight gain predicted the development of moderate-to-severe sleep-disordered breathing (defined by an AHI ≥15 events per hour of sleep) in individuals who initially had mild or no sleep-disordered breathing (AHI<7.5, Peppard et al 2000a). However, 28% (n=258) of the baseline sample could not be followed-up. A longitudinal bias may occur in these results because of incomplete follow-up.

Likewise, Redline et al (2003) monitored 486 individuals (mean age 32, 60% female) from the Cleveland Family Study who underwent 2 assessments over 5 years. They

reported that the prevalence of sleep-disordered breathing (defined by an AHI≥15) increased from 13.7% to 23.4% in men and from 8.3% to 11.4% in females. Median 5-year change in AHI changed nonlinearly with age (-0.1, 1.1, 2.3, and 0.9, for those < 18, 19-40, 41-54, and ≥55 years, respectively) and obesity (2.8 vs -0.1, for the top versus lowest BMI quartile). The authors concluded that older heavier men may experience the highest rate of increase in AHI over time In this study, patients who had been referred to a sleep laboratory or had received sleep-disordered breathing treatment were excluded. This may have caused bias in the estimates of longitudinal change. In a follow up study of 282 participants in the Wisconsin Sleep Cohort, there was a significant increase in RDI during 8 years. The overall mean AHI increased up to 2.6 events/hr, from 2.5 at baseline to 5.1 at follow up (Young et al 2002a). It should be noted that these studies show AHI progression not evidence of progression of OSAHS.

Tishler et al (2003) have directly evaluated the incidence of sleep-disordered breathing in a community-based sample of 286 adults aged 18 years or older. All participants who had 2 in-home sleep studies which were 5 years apart had an AHI < 5 at the baseline. They found that the 5-year incidence of mild to moderately-severe sleep-disordered breathing (AHI≥10) was 16% or less and it was about 10% for moderately-severe sleep-disordered breathing (AHI≥15). Two (4%) of 48 subjects with an initial AHI of at least 15 had second AHI values of less than 5. The authors suggested that approximately 2.5% of adults regress on second study from an AHI ≥ 15 to an AHI < 5. Thus, the overall 5-year incidence rate of AHI is reduced from 10% to about 7.5% for an AHI ≥ 15. In this study, although a change of AHI from less than 5 to a level of 5 to 9.9 may indicate progression of sleep-disordered breathing, the authors did not include such changes in the definition of incidence. Further, the incident of sleep-disordered

breathing was based on only AHI criteria, without including excessive daytime sleepiness or other symptoms. In two other studies, untreated patients with snoring or mild to moderate OSAHS were restudied 10 years and 17 months apart respectively, and a significant progression of sleep-disordered breathing was found in these patients (Lindberg et al 1999, Pendlebury et al 1997). Contrary findings were reported in another study of 32 patients with severe OSAHS who had undergone PSG five years before but had refused treatment and then had undergone a repeat PSG. It found that there was no change in AHI (mean AHI = 52) within the group. In fact, in some individuals, regression was seen after 5 years (Sforza et al 1994) which could have been due to regression to the mean. In these three studies, sample sizes were relatively small ($n < 55$), and the majority of subjects were men. These studies were retrospective, follow-up was incomplete and the conditions on the initial and follow up nights were not identical. For example, Pendlebury et al (1997) used oximetry and static charge sensitive bed screening on the first occasion but full PSG on the second occasion in the study. The alleged progression in the patient's clinical state may have been secondary to the use of PSG. Thus, the validity of these studies is questionable.

In conclusion, what data there is suggests that sleep-disordered breathing starts with simple snoring and develops into more severe forms of sleep-disordered breathing as is indicated by AHI. The mechanism of the progression of sleep-disordered breathing may involve local airway effects, obesity and advancing age. Prospective monitoring could theoretically be beneficial as regards the preventing a more serious form of sleep-disordered breathing in patients with mild to moderate OSAHS. Individuals who refuse treatment of sleep-disordered breathing may provide information on the natural history of untreated OSAHS. This issue is detailed later in section.

1.7 Predisposing Risk Factors for sleep-disordered breathing

1.7.1 Gender

Sleep-disordered breathing has been reported to be more frequent and severe in men than women, but recent studies have recognized that OSAHS among women is not as infrequent as was once believed (Bixler et al 2001, Chervin 2000). Although the estimated ratio of male/female has been reported as 8 to 10:1 in sleep laboratories (Guilleminault et al 1988, 1995, Redline et al 1994), in population-based studies this ratio is 2 to 4:1 (Young et al 1993, Bixler et al 2001).

The main reason for this discrepancy is alleged to be due to differences in clinical picture and characteristics of OSAHS experienced by men and women. Whereas male patients with OSAHS reported that they had loud snoring, witnessed apnoeas and excessive daytime sleepiness etc., females including those with severe OSAHS were more likely to complain about daytime fatigue, lack of energy, morning headache, depression and use of sedatives etc. (Redline et al 1994, Pillar and Lavie 1998, Chervin 2000).

Studies showed that obese and postmenopausal women are prone to experiencing severe sleep-disordered breathing (Young et al 1993, Bixler et al 2001, Young et al 2003). Pregnancy is also considered to be a period of particular risk for sleep-disordered breathing in women. This issue will be discussed further in chapter 3.

The predominance of sleep-disordered breathing in men rather than women decreases with increasing age, and after age 50 the occurrence of sleep-disordered breathing is similar between males and females (Tishler et al 2003). In the Wisconsin Sleep Cohort

study of 589 women between 30 and 60 years of age, including both longitudinal and cross-sectional data, Young and colleagues (2003) reported that the menopausal transition is a significant risk factor for sleep-disordered breathing for women, independent of known confounding factors such as age, BMI and other potential confounding factors. Postmenopausal women were 2.6 (95% confidence interval [CI]: 1.4-4.8) times more likely to have AHI ≥5 per hour and 3.5 (1.4-8.8) times more likely to have AHI ≥15 per hour than premenopausal women. The risk of sleep-disordered breathing, significantly, did not increase among primenopausal women.

In the Sleep Heart Health Study with a sample of 2,852 women, 50 years or older, 6.7% of 907 women receiving hormone replacement therapy (HRT) and 14.7% of 1,945 women without such replacement had an AHI >15. After adjusting for age, BMI, and other relevant possible confounders, there was an inverse association between hormone use and sleep-disordered breathing in various subgroups, especially in 50- to 59-year-old women (adjusted odds ratio 0.36; 95% CI 0.21-0.60) (Shahar et al 2003).

The analysis in the first study (Young et al 2003) is based on cross-sectional data which is associated with limitations and the findings could be limited by survivor bias due to women lost to follow-up. The changes in odds may reflect a survivor bias. In the second study (Shahar et al 2003), they did not have data on whether the women participating were menopausal or not at the time of the study, thus they were unable to assess the effect of menopause itself on sleep-disordered breathing. With both studies, as aging can have a significant effect on the prevalence of sleep-disordered breathing, it seems that these studies are unable to discern whether it is aging or the effect of menopause that is contributing to sleep-disordered breathing prevalence. Further, these two studies

provide no significant evidence regarding the mechanics of oestrogen and progesterone on apnoea pathophysiology, and thus give no clue as to whether HRT should be used routinely in clinics to prevent apnoea development or as therapy for sleep apnoea in postmenopausal women. A properly designed longitudinal study is needed to solve some of these problems.

Bixler and co-workers (2001) found that the prevalence of sleep apnoea in postmenopausal women without HRT was 2.7% which is significantly higher than the prevalence in postmenopausal women with HRT (0.5%) and premenopausal women (0.6%) and is more similar to the prevalence in men (3.9%). These results suggest that menopause is a potential risk factor for sleep-disordered breathing in women.
The effects of gender on UA size and on muscle activity of the UA are delineated in chapter 2.

1.7.2 Obesity

There is strong evidence that obesity is a causal factor for both snoring and OSAHS. Obesity is usually classified by the BMI kg/m^2. A person with a BMI of 30 or greater is considered obese. Young et al (1993) showed that an increase in BMI by one standard deviation (SD) was associated with a 4.5 fold increased risk of OSAHS. Peppard et al found that a 10% increase in weight was linked with a 6-fold greater risk of developing moderate or severe OSAHS among individuals who initially had mild or no sleep-disordered breathing in a longitudinal analysis of a subset of the Wisconsin cohort (Peppard et al 2000a). In our department, around 50% of patients with the OSAHS were reported to be technically obese (Mathur and Douglas 1995b, Douglas 2002).

However, it has been suggested that the effect of BMI decreases with age and may be negligible at age 60 years (Tishler et al 2003).

There is evidence that anthropomorphic measurements such as upper body obesity, neck circumference and waist-hip ratio (WHR) are better predictors of sleep-disordered breathing than BMI (Davies and Stradling 1990, Deegan and McNicholas 1996, Mortimore et al 1998, Fogel et al 2003a). The risk of sleep-disordered breathing tends to increase with upper body obesity in male and increasing neck size in both male and female patients (Deegan and McNicholas 1996, Mohsenin 2001). A neck circumference greater than 40.6 cm in a woman or greater than 43 cm in a man is associated with an increased risk for sleep-disordered breathing (Davies and Stradling 1990). It is possible that different types of fat distributions (e.g., central versus upper-body or neck obesity) are more important in specific subgroups such as male gender, pregnant female etc. Clinical interventions of obesity are explained in chapter 2.

1.7.3 Age

Sleep-disordered breathing is usually considered a disease of middle-aged adults between 30 and 65 years (Stradling and Crosby 1991), but studies have also shown that sleep-disordered breathing is very common in the elderly (age >65 years) (Bixler et al 1998, Bixler et al 2001, Young et al 2002b). An increased BMI, a reduction in UA muscle tone, thinning of the facial bones and loss of teeth that occur with age may all predispose to sleep-disordered breathing.

In older individuals (≥65 years) the prevalence of OSAHS has been reported to be 2- to 3-fold higher than in the middle aged adults (30-64 years) (Bixler et al 1998, Bixler et al

2001, Young et al 2002b). Severity of sleep apnoea has been found to decrease in older people (Ohayon et al 1997, Bixler et al 1998, Lindberg et al 1998b). In the Sleep Heart Health Study the correlation between age and AHI were weaker in older compared with middle-aged participants (Young et al 2002b). There was no association between sleep-disordered breathing and either cognitive functioning or hypertension (Lindberg et al 1998a, Foley et al 2003). An eighteen-year follow-up study by Ancoli et al indicated that changes in BMI were weakly associated with change in AHI in a sample of adults over the age of 65 years (Ancoli-Israel et al 2001).

1.7.4 Genetics / Ethnicity

Obstructive sleep apnoea has been reported in families, where more than one family member suffers from the disease (Mathur and Douglas 1995b, Redline et al 1995, Redline and Tishler 2000). The estimated risk of sleep apnoea was reported to be 2–4 fold greater in relatives of patients with sleep apnoea as compared to controls. Approximately 40% of the variance in AHI was explained by familial factors (Redline and Tishler 2000).

Recent studies have shown that risk factors for sleep-disordered breathing differ between different ethnic groups. Craniofacial bony structure is a relatively important risk factor for sleep-disordered breathing in people with Chinese and other Far Eastern origin (Lam et al 2005). In a prospective nonrandomized controlled study, Li et al (2000) observed that Asian men with OSAHS have more severe OSAHS and less obesity than Caucasian. OSAHS among Asian groups appears to be related to different craniofacial morphology (the cranial base dimensions were significantly decreased) than that associated with OSAHS in Caucasians (Li et al 2000).

1.8 Pathogenesis of sleep disordered breathing

The pathogenesis of sleep-disordered breathing is a complex issue and remains only partially understood despite the high prevalence of sleep-disordered breathing. It likely occurs in different patients for different reasons. Current understanding of the pathologic characteristics of sleep-disordered breathing suggests that partial or complete UA obstruction at the pharyngeal level plays an important role in pathogenesis of sleep-disordered breathing (Deegan and McNicholas 1995). Issues related to UA are detailed further in the second chapter of this thesis.

1.9 Clinical Presentations

1.9.1 Nocturnal features

●**Snoring:** Snoring is considered an essential part of each phase along the continuum of sleep-disordered breathing. Almost all patients with OSAHS snore (Whyte et al 1989), but by no means all snorers have these severe forms of sleep-disordered breathing. Snoring generally arises in the supine position, but habitual snoring occurs in all body postures (Whyte et al 1989, Bassiri and Guilleminault 2000, Guilleminault and Abad 2004). Weight gain increases the volume of snoring. It is common among pregnant women in the third trimester of pregnancy (Loube et al 1996, Franklin et al 2000, Edwards et al 2000a, Connolly et al 2001). Sore throat, dry mouth and drooling are frequent consequences of snoring and mouth breathing during sleep (Guilleminault and Abad 2004).

Loud intrusive snoring is a major inconvenience and affects bed partners and other family members. Many couples sleep apart because of it (Izci et al 2005). For these reasons, a partner will very often force his/her partner to find medical help.

●Witnessed apnoeas and nocturnal choking: UA narrowing and occlusion often cause the transient reduction in, or cessation of, breathing which results in hypoxemia and partial arousal. These respiratory episodes are often followed by a kind of explosion of pharyngeal noise and also by bodily movements. Those who suffer in this way may be awakened with a choking sensation and sometimes experience nocturnal panic and chest discomfort (tachycardia) (Douglas 2002). Eighteen to 31% of patients with OSAHS reported that their sleep was interrupted by an awareness of choking or breathlessness (Whyte et al 1989, Bassiri and Guilleminault 2000). These events frequently produce the greatest amount of concern from partners rather than from the patients themselves.

●Restless sleep: Increased respiratory effort and arousals are perhaps the cause of sweating in the neck and upper chest area, restlessness with tossing and turning in bed, and the feeling of being unrefreshed after the night's sleep (Bassiri and Guilleminault 2000, Guilleminault and Abad 2004). Thirty-five percent of patients with OSAHS reported unsatisfying sleep (Whyte et al 1989). Most patients with UARS complain about insomnia due to problems with sleep maintenance or unrefreshing sleep (Guilleminault and Abad 2004).

●Nocturia: Nocturia is a common symptom of sleep-disordered breathing (Warley et al 1988). It has been reported that augmented generation of atrial naturetic peptide, a diuretic hormone, due to hypoxia and the increased negative intrathoracic pressure is the main reason of increased urine production during sleep in patients with sleep-disordered breathing (Kinn and Harlid 2003). This symptom also is a very common problem in pregnant women in the third trimester of pregnancy, probably due to a

combination of increased incident of sleep-disordered breathing and an enlarging uterus. Thus, recurrent awakenings due to the need to visiting the bathroom may often play a role for daytime sleepiness.

●Nocturnal gastro-oesophageal reflux: Patients with sleep-disordered breathing have a high incidence of nocturnal gastro-oesophageal reflux (e.g. dysphagia and heartburn) due to negative intra-thoracic pressure (Deegan and McNicholas 1996) during apnoeas and arousals. Deegan and McNicholas (1996) stated that "patients with OSA tended to be more obese with thicker waists, which would predispose to gastric acid reflux". CPAP treatment may lessen the frequency and length of nocturnal reflux incidents.

1.9.2 Daytime Symptoms

●Daytime Sleepiness: Uncontrollable sleep during the day, or excessive daytime sleepiness, is the principal daytime manifestation of sleep-disordered breathing. Even snoring alone, without OSAHS, may produce daytime sleepiness. Stradling and coworkers (1991) reported that self-reported snoring (often) correlated significantly with uncontrollable sleep during the day, after adjusting for the severity of sleep-disordered breathing (defined by the frequency of 4% dips in oxygen saturation during sleep). The risk of having excessive daytime sleepiness was increased by 6-fold in an "often" snorer. Sleepiness generally occurs in monotonous situations such as watching television or films, sitting as a passenger in a car, attending meetings or conferences, eating, working for a long time with computers or while driving (Bassiri and Guilleminault 2000, Douglas 2002, Guilleminault and Abad 2004).

Most patients with OSAHS and individuals with suspected OSAHS report sleepiness (Whyte et al 1989, Douglas 2002), although to some extent this is a self-fulfilling prophesy as many define OSAHS as sleep-disordered breathing plus sleepiness (Stradling and Crosby 1991, Jennum and Sjol 1992, Young et al 1993, Bearpark et al 1995, American Academy of Sleep Medicine Task Force. 1999, Douglas 2002). In some cases, patients, particularly with undiagnosed sleep-disordered breathing may underreport their sleepiness, perhaps because they lose their frame of reference for abnormal sleepiness (Douglas 2002), possibly due to having this problem for a long time. In other circumstances, they can deny it because of social pressures (e.g. the danger of losing their job). Excessive daytime sleepiness also may be attributed to other reasons such shift work. Therefore, the prevalence of excessive daytime sleepiness can be higher than these estimations. Conversely, some asymptomatic individuals do not experience excessive daytime sleepiness. Young et al (1993) found that 20% of men and 7% women had an AHI≥5 but were not sleepy, and this is around 5 times as many as had AHI>5 and sleepiness. Excessive daytime sleepiness is determined by from history and by objective testing, such as the MSLT, which is conventionally preceded by an overnight PSG to document adequate sleep.

●Unrefreshing nighttime Sleep: Excessive daytime sleepiness is often associated with unrefreshing nighttime sleep. Patients with sleep-disordered breathing often suffer from unrefreshing sleep, irrespective of how many hours they sleep (Whyte et al 1989, Young et al 1993). Unrefreshing nighttime sleep is probably due to recurrent cortical arousals at the end of apnoeas/hypopnoeas, or microarousals (RERAs) due to increased upper-airway resistance (Stradling and Davies 2004). Patients generally are not aware of these brief arousals during sleep (Douglas 2002).

●Impaired Concentration: Excessive daytime sleepiness, impaired concentration and snoring are the dominant symptoms of sleep-disordered breathing. Sleepiness has a major effect on concentration, memory, judgment and cognitive performance of tasks requiring dexterity and alertness (Cheshire et al 1992, Bassiri and Guilleminault 2000).

●Emotional Problems: Sleepiness can result in personality changes, mood disturbance and most importantly depression, the last of these being a common problem in patients with OSAHS. (Cheshire et al 1992, Bassiri and Guilleminault 2000, Wells et al 2004). However, depression itself impairs sleep quality and cognitive performance (Cheshire et al 1992, Wells et al 2004). Therefore self-reported sleepiness and impaired concentration may be misdiagnosed and attributed to depression.

●Decreased libido/impotence: Decreased libido/impotence is common among patients with OSAHS. Six percent to 33 % of patients with OSAHS in case series reported sexual dysfunction, either decreased libido or impotence (Whyte et al 1989, Bassiri and Guilleminault 2000).

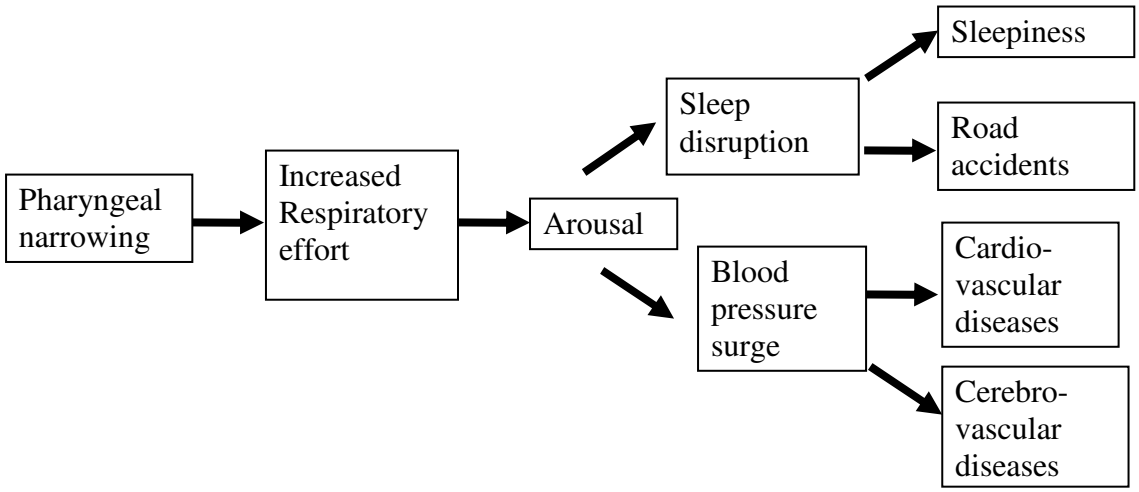
●Headache: Approximately 50% of patients with OSAHS complain of repeated morning headache, but there has been considerable debate and conflicting data as to whether this is a real association (Guilleminault et al 1976, Bassiri and Guilleminault 2000, Douglas 2002).

1.10 Consequences and associations of OSAHS with other conditions

The short-term consequences of UA obstruction during sleep include arousals, sleep fragmentation, intermittent hypoxemia and hypercapnia, and nocturnal blood pressure

surges. The long-term complications of OSAHS are important and may contribute to mortality: hypertension, cardiovascular, and cerebrovascular diseases. Some neurobehavioral morbidities such as daytime sleepiness and impaired cognitive function are also linked with OSAHS and may contribute to motor vehicle crashes and work-related accidents in untreated patients with OSAHS (Young et al 2002a). This thesis focuses on cardiovascular diseases, especially hypertension, due to its relation with pregnancy induced hypertension.

Figure 1.1 Schematic diagram of the consequences of upper airway narrowing in the OSAHS. *(From Douglas NJ, Lancet 1994; 344(8923):653-5)*



1.10.1 OSAHS as a Risk Factor for Hypertension

Studies performed in normal populations (Ringler et al 1994, Bixler et al 2000, Nieto et al 2000, Peppard et al 2000b) and patients with snoring and OSAHS (Grote et al 1999, Davies et al 2000, Lavie et al 2000, Stradling et al 2000, Moller et al 2003) have demonstrated, after adjusting for obesity and other lifestyle factors, that sleep-disordered breathing is an independent risk factor for both nocturnal and diurnal hypertension.

It is generally believed that altered peripheral chemoreceptor sensitivity and increased sympathetic activity triggered by intermittent hypoxemia, baroreceptor desensitization, intrathoracic pressure swings, and arousal from sleep may underlie the association between sleep-disordered breathing and hypertension (Fletcher 2000, Moller et al 2003, Heitmann et al 2004, Guilleminault and Abad 2004, Ryan et al 2005). The repeated changes of oxygen saturation could be considered similar to recurrent episodes of ischemia-reperfusion injury, which causes damage after the restoration of blood flow to ischaemic or hypoxic tissues (Ryan et al 2005). Such damage has been ascribed to the production of reactive oxygen species (ROS) during reoxygenation (Lavie 2003) although this has recently been challenged (Svatikova 2005). The hyperoxia, hypoxia, and oxygen free radicals may cause damage to endothelial and vascular smooth muscle cells, which can directly and indirectly alter hormones, enzymes, and growth factors that affect vascular remodelling, reactivity and tone in resistance vessels (Fletcher 2000). Thus, endothelial dysfunction may lead to the abnormal regulation of blood-vessel tone, peripheral vasoconstriction, potentially hypertension and adverse cardiovascular outcome (Lavie 2003). These factors were also reported to play an important role in the pathogenesis of preeclampsia, which is detailed in chapter 3.

It has been reported that the association between sleep-disordered breathing and hypertension may occur in snorers with undiagnosed OSAHS or in non-apnoeic snorers who may have UARS (which could contribute to hypertension) (Lindberg et al 1998a). This association between hypertension and the degree of sleep-disordered breathing is confirmed in several large cross-sectional studies (Nieto et al 2000, Bixler et al 2000).

The Sleep Heart Health Study on 6,132 individuals indicated that sleep-disordered breathing is associated with systemic hypertension in middle-aged and older individuals of both sexes, different ethnic backgrounds and among normal-weight and overweight individuals. The prevalence of hypertension increased considerably with increasing sleep-disordered breathing measures, but some of this association was explained by BMI. The odds ratio for hypertension, comparing the highest category of AHI (≥30 per hr) with the lowest (<1.5 per hr), was 1.37 (95% CI, 1.03-1.83) after adjusting for BMI, neck circumference, waist-to-hip ratio, alcohol intake and smoking (Nieto et al 2000).

Although these results show an association between sleep-disordered breathing events and hypertension, it cannot be expected to prove causality due to nature of this cross-sectional cohort study. Additionally, if sleep-disordered breathing is linked with increased mortality, the survival of a hypertensive individual with sleep-disordered breathing would tend to be shorter than that of one without sleep-disordered breathing. Thus, the cross-sectional estimates in this study might underestimate the true relative risk. It is also possible that selection biases occur due to the volunteer character of the sample, who may have prior knowledge of blood pressure abnormalities.

Likewise, an association between sleep-disordered breathing and hypertension has been found in a 4 year follow-up of the Wisconsin Sleep Cohort Study of 790 subjects after adjustment for BMI, age, sex, and cigarette and alcohol use. The odds ratios for hypertension at follow-up was 1.42 (95 % CI, 1.13 to 1.78) in individuals with AHI of 0.1-4.9 per hour at baseline as compared with those with AHI=0. Individuals with AHI ≥5-14.9 (mild sleep-disordered breathing) and those with AHI≥15 (more severe sleep-disordered breathing) had approximately two and three times, respectively, the risks of

having hypertension at follow-up compared with those with AHI=0 (Peppard et al 2000b). Even though this prospective study supports the evidence of a causal role of sleep-disordered breathing in hypertension, these data need to be interpreted with caution as the initial health screening and sleep study result at baseline may have precipitated some of these diagnoses of hypertension being made.

Davies et al (2000) very carefully matched 45 OSA patients with 45 nonapneic control subjects for age, BMI, alcohol, smoking, treated hypertension, and ischaemic heart disease and examined their 24-hour blood pressure. They found that daytime and nighttime diastolic as well as nighttime systolic blood pressure were significantly higher in patients with OSA than in the control subjects. However, daytime naps of hypersomnolent OSA subjects were not recorded. This may have falsely lowered their daytime blood pressure compared with those of the control subjects. Thus, daytime differences in both the systolic and diastolic blood pressures may be greater than were reported.

In our department, in a randomized placebo controlled crossover study of CPAP therapy in 68 OSAHS patients average 24 hour diastolic blood pressure decreased by 1.5 mmHg over 4 weeks. This effect was primarily attributed to improvements in nocturnal blood pressure (between 2 am and 9:59 am). The greatest effect was seen in two groups: CPAP use >3.5 hours per night and those with 4% desaturation frequencies above 20 per hour on the baseline sleep studies. The falls in blood pressure were greater in the latter group in whom systolic pressure over 24 hour dropped by 4 mm Hg and diastolic pressure by 5 mm Hg. The relatively small effects of CPAP on overall blood pressure in

the total group may have been explained by the fact that most of the patients studied did not exhibit significant nocturnal hypoxaemia (Faccenda et al 2001).

In a controlled parallel designed trial of 118 patients with OSAHS who were assigned to either therapeutic (n=59) or subtherapeutic (n=59) CPAP (about 1 cm H2O pressure), CPAP reduced mean arterial ambulatory blood pressure by 2.5 mm Hg over 4 weeks. There was a significant fall from baseline of 3.3 mm Hg in mean ambulatory blood pressure in patients with moderate or severe OSAHS when given therapeutic CPAP compared with patients on subtherapeutic CPAP. This benefit was seen in both systolic and diastolic blood pressure, and during both sleep and wake. The effect was most pronounced in patients with severe OSAHS and hypertension (6.6 mmHg fall in mean systemic blood pressure) (Pepperell et al 2002). These results are compatible with those of previous studies. However, it is questionable whether a sham CPAP is an ideal placebo for several reasons. First a subtherapeutic CPAP may falsely increase blood pressure due to possibly keeping the patient awake. Secondly, if patients don't obtain benefit from sham CPAP, they may not use it as much as real CPAP. Thus it would not have a true placebo effect at the end of the study. Next, subtherapeutic CPAP pressure might maintain the airway patency sufficiently to treat some episodes of UA narrowing (Faccenda et al 2001).. However there are also disadvantages to tablets as a placebo for a machine and there is no perfect placebo for CPAP therapy.

Becker et al (2003) evaluated 60 consecutive patients with moderate to severe OSA (defined as AHI>5 and ESS >10) who were not stratified according to AHI. Patients were randomly assigned to either therapeutic or subtherapeutic nCPAP over a 9-week average period. There was a very large reduction in mean arterial pressure of 9.9 mm Hg

in the therapeutic nCPAP group (during the day and night), but an increase by 0.6 mm Hg in the subtherapeutic group. Both diastolic and systolic blood pressures also deceased by 10.3 mm Hg and 9.5 mm Hg, respectively, with therapeutic nCPAP compared with subtherapeutic nCPAP. Although the findings of this study are impressive, it was limited by a large dropout rate of 49% for technical reasons and its applicability limited by the in-patient nature of the trial.

Additionally a randomized controlled trial has shown that oral appliances may also reduce blood pressure in OSAHS (Gotsopoulos et al 2004). The decrease in blood pressure found with the oral appliance was similar to that which would have been obtained by CPAP in similar patients (Douglas 2004).

In an age-matched case-control series Moller et al (2003) compared 24 hour blood pressure and plasma levels of the vasoactive hormones (renin, angiotensin II, aldosterone, atrial natriuretic peptide, brain natriuretic peptide, vasopressin, and endothelin-1) in 24 patients with OSA and in 18 control subjects. Additionally, the same variables were compared in 13 patients before and after 14 months of CPAP therapy. They found that patients with OSA had elevated diurnal and nocturnal blood pressure, and that plasma angiotensin II was positively correlated with blood pressure. A strong correlation also has been found between the blood pressure reduction and decreased activity in the renin-angiotensin system after successful CPAP treatment. The authors suggested that "OSA mediates hypertension, at least in part, via a stimulation of angiotensin II production". However, the absence of sleep disordered breathing was not documented objectively in the control subjects. Thus, not being able to take this information into account, the findings of the study are somewhat weakened or, perhaps,

findings may be biased by the existence of control subjects with asymptomatic OSA. Obesity also could have a confounding effect on the results because patients with OSA had greater BMIs than the controls.

Heitmann et al (2004) also prospectively studied the effect of nCPAP on noradrenaline plasma levels, blood pressure and heart rate in 10 normotensive and age matched eight hypertensive patients with OSAHS before and after 42 days of CPAP treatment. They showed a significant reduction in noradrenaline, blood pressure in both day- and nighttime, which reduced in a similar range, and heart rate in hypertensive but not in normotensive OSAHS patients with nCPAP. These results suggest that sympathetic activity in hypertensive OSAHS patients, which occurred during both day- and nighttime, can be decreased by nCPAP. However this study has some methodological limitations, including the lack of randomisation or control treatment, lack of a healthy control group, and the hypertensive group was more severe and obese than normotensive group at baseline. In addition to this, in the study inclusion if a patient's daytime average blood pressure in the ambulatory blood pressure measurement was ≥135/85 mmHg, they were assigned to the hypertensive group, if less, the normotensive group. This procedure caused a considerable overlap in measured blood pressure during the baseline measurement between the two patient groups. Therefore all these factors may have affected the main results of this study.

The findings from the epidemiological data are consistent, but these studies cannot prove a causal link. They are also potentially limited by the fact that the PSGs were done at home and that the population was selected from patients seeking OSA evaluation, which limits the ability to generalize the findings. Interventional clinical trials can

generally overcome the potential confounding factors but need to be controlled in terms of placebo use and randomisation. The general conviction expressed in these studies is that patients with either more severe hypertension or moderate to severe OSA can benefit from treatment of sleep-disordered breathing. However, blood pressure is a continuum and blood pressure reduction at any level of starting blood pressure may lead to a substantial reduction in cardiovascular risk.

1.10.2 Other cardiovascular diseases

OSAHS is associated with increased cardiovascular morbidity and mortality independent of confounders. However definitive data firmly establishing a relationship between sleep-disordered breathing and cardiovascular disease are lacking. There is the convincing idea that sleep-disordered breathing could directly contribute to atherogenesis. As mentioned above, the repeated deoxygenation/reoxygenation that occurs in sleep-disordered breathing, might initiate oxidative stress. The possible mechanism involved in this is summarized in a review article by Lavie (2003). In patients with untreated sleep-disordered breathing, oxidative stress, which is associated with endothelial dysfunction occurring for many years, may play a role in the onset of cardiovascular complications (Lavie 2003, Ryan et al 2005, Svatikova 2005). Endothelial dysfunction and oxidative stress are also reported to be associated with cardiovascular disease in the later life of pre-eclamptic women (Roberts and Lain 2002, Duley 2003, Longo et al 2003). Further studies are needed if this association between sleep-disordered breathing, pre-eclampsia and cardiovascular disease is to be clarified.

Nieto and colleagues (2004) examined the association between sleep apnoea and endothelial dysfunction using high-frequency ultrasound to measure flow-mediated

vasodilation in a large scale Sleep Heart Health Study of 1,037 mostly asymptomatic subjects with variable degrees of sleep-disordered breathing, age >68 years. They reported a statistically significant linear association between the hypoxemia index and the baseline brachial artery diameter after adjustment for BMI and other confounders such as age and sex. These results suggest that sleep apnoea–associated hypoxemia might be associated with endothelial dysfunction. The possibility of selection bias in this study may affect the association between hypoxemia index and brachial ultrasound measures because of surviving volunteer participants who agreed to undertake the brachial ultrasound and home PSG.

In the Sleep Heart Health Study of 6,424 individuals who underwent unattended overnight PSG at home, 1,023 participants (16%) reported at least one manifestation of cardiovascular disease. The median AHI was 4.4 (interquartile range, 1.3 to 11.0). Compared with the first quartile for the AHI (<1.4), the relative risks for cardiovascular disease were 0.98 (0.77-1.24) for the second quartile (AHI of 1.4 to 4.4), 1.28 (1.02-1.61) for the third quartile (AHI of 4.5 to 11), and 1.42 (1.13-1.78) for the fourth quartile (AHI>11). The odds ratios were 2.4 (1.22-4.62) for heart failure, 1.6 (1.02- 2.46) for stroke and 1.3 (0.99-1.62) for cardiovascular disease in those with an AHI>11 in comparison to those with an AHI<1.4 after controlling age, gender, smoking, obesity, hypertension, and diabetes (Shahar et al 2001). The authors conclude that sleep-disordered breathing with indexes normal or mildly elevated has a modest to moderate effect upon the presence of symptoms of cardiovascular disease. This cross-sectional data from the study typically may cause the underestimation of the incidence odds due to survival bias. Also, the results of this study may be influenced by inaccurate self-reported cardiovascular disease at baseline.

In a follow-up study on a retrospectively selected consecutive sleep clinic cohort of 182 middle-aged men (aged 30–69 years) with or without OSA, the incidence of cardiovascular disease over 7 years was 37% (n=22) in patients with OSA (n=60) compared with 6.6% (n=8) of those without OSA (n=122). Cardiovascular disease incidence was much higher in patients who were incompletely treated for their OSA (56% over 7 years) than in those who were effectively treated (6.7%) This data suggest that incompletely treated OSA is an independent risk factor for incident cardiovascular disease after controlling for potential confounders. "OSA patients without any treatment or with remaining OSA despite treatment with UPPP, or oral device or daily CPAP run time of less than 50% of estimated sleep time were regarded as incompletely treated". In this study the diagnosis of OSA was mainly based on the oximetry results, data from oro-nasal thermistors and respiratory and body movements at baseline. Thus, OSA subjects with dominantly hypopnoeas may likely have not been diagnosed due to the absence of significant desaturations. Apnoea index may not be the most relevant pathophysiologic feature of OSA contributing to cardiovascular disease (Peker 2002).

Using snoring as a marker of a less severe form of sleep-disordered breathing, the Nurses' Health Study, an 8 years follow-up study of more than 10,000 female nurses, demonstrated that relative risks of cardiovascular disease were 1.5 (95% CI, 1.23 -1.74) for occasional snorers and 2 (1.62 - 2.53) for habitual snorers compared with nonsnorers after the age-adjustment. After further adjustment for smoking, BMI and other confounding factors, although the positive association between snoring and cardiovascular disease was decreased, it still was statistically significant: 1.2 (1.01 - 1.43) for occasional snorers and 1.33 (1.06–1.67) for regular snorers (Hu et al 2000). In this study, the reliability of snoring which was reported by female nurses, was not validated.

If subjects were unaware of their snoring this could lead to an underestimation of the effects of snoring on cardiovascular disease.

Gami and colleagues (2004) reported a strong association between OSAHS and atrial fibrillation in a prospective study that OSAHS is strikingly more prevalent in patients (n=151) with atrial fibrillation (49%) than in age, gender, BMI, blood pressure, diabetes, and congestive heart failure matched patients (n=312) with many other cardiovascular diseases (32%).

Milleron et al (2004) performed a prospective study to evaluate the effect of OSA treatment on the rate of cardiovascular events in coronary artery disease in 54 patients diagnosed with both coronary artery disease and OSAHS (AHI>15). Twenty-one patients underwent CPAP therapy, four underwent OSAHS surgery, and 29 had no treatment for OSAHS (followed for a median of 86.5 months). Patients treated for OSAHS had a significantly reduced risk of cardiovascular death, acute coronary syndrome, hospitalization for heart failure, and the need for coronary revascularization compared to patients who had no treatment for OSAHS. The absence of randomisation together with a modest number of patients limits this study.

Two randomized controlled trails have shown an improvement in heart function with CPAP (Kaneko et al 2003, Mansfield et al 2004). In the study by Kaneko et al. (2003), 24 patients with OSAHS and co-existing heart failure were randomized to one month of CPAP or medical therapy. An improvement of 8.8% in left ventricular ejection fraction was observed in the group treated for one month. Mean systemic blood pressure also decreased by 10 mmHg. In a larger study of 55 patients who were randomized to 3

months of CPAP or control groups, Mansfield et al (2004) showed a 5% improvement in patients with less severe Congestive heart failure (CHF) and mild to moderate OSA. This improvement was associated with a one third fall in overnight urinary catecholamine excretion and improved quality of life scores. These studies are small, but their results are promising.

In summary, there is strong evidence for an association between OSAHS and cardiovascular diseases, and this evidence is particularly robust for the link with hypertension. This association occurs possibly due to increased sympathetic activity or atherogenesis (or both), as free radical production occurs in OSAHS as a consequence of the cyclic deoxygenation/ reoxygenation. The treatment of OSAHS can significantly decrease the risk of cardiovascular disease. However, there are no clear data showing the long term benefit with regard to cardiovascular end points with CPAP therapy. Thus, future studies, perhaps larger randomized controlled trials, will have to prove the beneficial effects of CPAP treatment on cardiovascular outcome parameters in sleep-disordered breathing. However, using sham CPAP during the long period to assess clinical endpoints appears to be ethically questionable.

1.11 Mortality

Uncontrolled or non-randomised studies have indicated that the risk of mortality increases in untreated patients with moderate or severe forms of sleep-disordered breathing particularly in males aged <50 years in comparison with the general population and patients who are treated for sleep-disordered breathing (Lavie et al 2005, Marin et al 2005, He et al 1988). The effect of treatment on mortality in sleep apnoeic patients has not been widely studied.

In a study by He and coworkers (1988), mortality in treated versus untreated patients was compared in the 385 patients. The possibility of eight-year survival was 0.96 (SE± 0.02) for an apnoea index less than 20 compared to 63 (0.17) for an apnoea index greater than 20. Patients with apnoea index greater than 20 and those treated by uvulopalatopharyngoplasty (UPPP) had a greater mortality than those with apnoea index less than 20 and those treated by either tracheostomy or CPAP. This study compared survival between self-selected groups which were not randomised. Further it was based on small sample size and apnoea index without recording hypopnoea, and did not examine the contributing role of obesity. These factors limit the applicability of the study's results.

Partinen and Guilleminault (1990) performed 7-year morbidity analysis of 198 patients with sleep apnoea in a retrospective study. They found an increased death rate in conservatively treated patients with OSAHS, when compared with those who were treated with tracheotomy after adjustment for BMI and age. However again this study was not randomised and, at entry, 56 percent of the population already had a vascular problem, particularly hypertension. This weakens the results.

In a prospective cohort study, 408 patients aged 70 yr or younger with coronary disease were followed for a median period of 5.1 year. It was demonstrated that an oxygen desaturation index≥5 and an AHI>10 events/hr predicted a 70% and 62% (respectively) relative increase in the composite risks of occurrence of death, cerebrovascular events, and myocardial infarction (Mooe et al 2001). In this study, EEG was not recorded and sleep time was estimated with the pressure-sensitive bed which is associated with its limitations. The different types of apnoeas were not distinguished.

However, poor left ventricular function with congestive heart failure may be associated with the central apnoeas without breathing efforts. The prediction of risk of death and cardio vascular disease regarding of AHI can be lower than 62 %.

Veale et al (2000) also analyzed mortality in a large sample (5,669 patients) of OSAHS patients comparing patients dying on CPAP (n=124) with age and sex matched patients (n=123) who started to use CPAP at the same time. A survival rate was found of 90% at 6 years, which is the same in the general French population, but compliance with CPAP was significantly worse in patients who died. The proportion of patients with cardiovascular diagnoses such as dysrhythmia; ischaemic diseases and cardiac failure was higher in the group dying on CPAP. The main problem with this study is that the benefit of CPAP in improving mortality was only indirectly evaluated by means of comparison with the general population without assessing symptom relief. Also authors reported that they had less compliance data in the death group, due to early CPAP machines which did not recode compliance data. This may present a degree of bias to the collected data in this study.

Lavie et al (2005) conducted a follow-up mortality study in a large cohort of 14,589 males, aged 20–93 years, who were referred to the sleep clinics with suspected sleep-disordered breathing or diagnosed with sleep apnoea in Israel. Altogether, 372 deaths were recorded after a median follow-up of 4.6 years. The all-cause mortality rate was 5.55/1,000 patient years, increasing with apnoea severity and high BMI. Comparing mortality rates of males with moderate/severe sleep apnoea to the general population indicated that only males aged <50 years showed an excess mortality rate. In this study other potential confounding factors apart from age and BMI at the time of diagnosis

and treatment of the syndrome were not controlled. The effect of treatment on mortality was also not investigated. Thus, when interpreting these results, consideration must be given to the lack of information about possible confounders and treatment effects.

Doherty et al (2005) performed a long-term follow-up study of 168 patients to compare survival between patients who were compliant with (n=107) or intolerant of CPAP (n=61) over an average 7.5-year period. Despite the untreated group having less severe sleep apnoea, the mortality rate was 14.8% compared to the CPAP tolerant group of 1.9%. Again the authors did not randomize their patients for the treatment and the control groups were those who were not compliant with CPAP therapy. In general these noncompliant patients might be less adherent to treatments such as cardiovascular medication, and general dietary and lifestyle advice for reasons such as presence of comorbidities. Therefore noncompliant patients may not serve as a proper control group. Only a part of the study population (n=144) was also followed up prospectively and the remaining patients (n= 24) were included at a later date. This can be a confounding factor. The study was also relatively small.

Campos-Rodriguez et al (2005) investigated mortality over a 5-year period in 871 patients with OSA (80.9% men, mean age=55.4) who had been offered PAP treatment (CPAP or bilevel pressure ventilation). Survival among the PAP non-compliant group was significantly lower than in the compliant group (85.5% versus 96.4%, p=0.01). The main variable that independently predicted death before the commencement of PAP therapy was cardiovascular disease. Compliance of PAP, arterial hypertension, predicted forced expiratory volume in 1 second (FEV1) values and age were the other predictors

of death before the start of treatment. In this study the control group was made up of noncompliant patients, who have the same limitations mentioned above. Authors also did not assess whether these patients were using the appropriate medication for arterial hypertension and complied with that treatment, which could have influenced their mortality.

Marin et al (2005) recruited and followed-up 264 healthy men, 377 simple snorers, 403 patients with untreated mild/moderate sleep apnoea, 372 patients with severe OSA compliant on CPAP and 235 patients with severe OSA unable to comply with CPAP (age and BMI matched) over a 10.1-year (on average) period. Multivariate analysis, adjusted for potential confounders such as age and BMI showed that untreated patients with severe obstructive sleep apnoea-hypopnoea had significantly increased the risk of fatal (odds ratio 2.87, 95%CI 1.17-7.51) and non-fatal (3·17, 1.12-7.51) cardiovascular events compared with healthy participants. Simple snorers did not appear to have excess mortality. This study was not randomised. It also used untreated patients as a control group. These are associated with the limitations in the studies mentioned above. However the results are fairly convincing.

In summary, these studies suggest, but do not prove (due to study design; such as for instance a retrospective study) a relationship between sleep-disordered breathing and excess mortality. In some cases confounding variables were not controlled adequately. In most cases there was not a proper control group. The comparator of untreated sleep-disordered breathing due to compliance problems can cause an unmeasurable study bias. This can exaggerate the findings. Further, well-controlled studies are needed to establish the effect of treatment on the longevity of sleep apnoea patients. The ideal

study that randomizes patients with OSA to treatment (including oral appliances and UPPP) or no treatment poses an ethical challenge.

In addition to the above-mentioned secondary medical conditions, sleep-disordered breathing -related motor vehicle crashes and work accidents in untreated/undiagnosed patients are important possible causes of increased mortality rate (Young et al 2002a).

1.12 Diagnosis of sleep-disordered breathing

A comprehensive history and careful physical examination are critical to exclude other causes for the patient's symptoms and determine whether a further sleep study (overnight PSG) is necessary before initiating treatment (Douglas 2002).

1.12.1 History

A careful history can provide clues to the diagnosis of sleep-disordered breathing. OSAHS should be differentiated from other disorders associated with loud snoring and daytime sleepiness. Primary snoring is characterized by snoring only and is not associated with excessive daytime sleepiness (American Academy of Sleep medicine 2001). Excessive daytime sleepiness may occur due to other sleep disorders, psychiatric disorders, drugs, environmental factors, and hormone-related conditions such as pregnancy and menstruation. For example, 40% of individuals without sleep-disordered breathing in a community-based, albeit Spanish, study reported having excessive daytime sleepiness (Duran et al 2001). Therefore both snoring and excessive daytime sleepiness may be poor discriminators of OSAHS.

Patients are often unaware of their symptoms. A patient generally does not either experience his/her snoring or is not aware of any unpleasant affects from his/her snoring other than the annoyance reported by others. Some other groups with OSAHS or UARS might not snore or might deny snoring and sleepiness for various reasons. The frequency of snoring, breathing pauses, postural dependence (lying on side or supine), restless sleep and daytime sleepiness are best confirmed by the bed partner or the patient's family (American Sleep Disorders Association 1997, Douglas 2002, Young et al 2002b). Thus the opinions of bed partners are necessary and often very helpful. A community epidemiological study showed that the prevalence of snoring increased from 10% to 23% when the partner joined the interview process (Stradling and Crosby 1991).

1.12.2 The Physical Examination

The examination only provides guides to therapy rather than diagnostic information in terms of sleep-disordered breathing. Physical assessments of sleep-disordered breathing should include recording blood pressure, BMI, neck circumference (Mortimore et al 1998), jaw structure such as retrognathia, tongue size e.g. macroglossia, tonsillar enlargement, nasal polyps, septal deviation, uvula shape (size and length) (Bassiri and Guilleminault 2000, Douglas 2002, Scottish Intercollegiate Guidelines Network 2003), and the presence of inflammation in the UA structures. The existence of significant cardiovascular, respiratory and neurological co-morbidity should also be clarified (Douglas 2002, Scottish Intercollegiate Guidelines Network 2003). Signs of other predisposing conditions should be identified e.g. the possibility of hypothyroidism, acromegaly and Marfan's syndrome (Douglas 2002, Scottish Intercollegiate Guidelines Network 2003).

1.12.3 Objective Techniques for Diagnosis

Full-night or split night full PSG, limited PSG, or oximetry alone are used in clinical practice (American Sleep Disorders Association 1997). These simple or complex studies can be applied either in hospital or at home (Scottish Intercollegiate Guidelines Network 2003). Full-night PSG,—a laboratory-based, multimodal recording of sleep architecture—is considered the gold standard for diagnosis of a wide range of sleep disorders but there is no evidence that it is needed to diagnose sleep-disordered breathing (American Sleep Disorders Association 1997, Hosselet et al 2001, Douglas 2002).

The use of PSG for evaluating sleep-disordered breathing usually involves recording the following channels: electroencephalography (EEG), electro-oculography (EOG), chin electromyography (EMG), air-flow (by nasal and oral thermistor or pressure), arterial oxygen saturation (by oximetry), respiratory effort (by thoracoabdominal inductance plethysmography), electrocardiography (ECG), limb movements (by lower extremity EMG), body position (lateral decubitus vs supine) and snoring (American Sleep Disorders Association 1997, Douglas 2002, Scottish Intercollegiate Guidelines Network 2003). Esophageal pressure (Pes) during PSG recording is the reference standard for measuring respiratory effort (American Academy of Sleep Medicine Task Force 1999, Hosselet et al 2001). Nasal cannula/pressure is more sensitive than thermistors for detecting respiratory changes including RERAs. However, its sensitivity has been shown to be less than Pes measurement (Rees et al 2000).

Sleep quality and stages are analysed using an agreed criteria developed by Rechtschaffen et al. (1973). Respiratory events and other related events are scored using

American Academy of Sleep Medicine Task Force (1999) criteria and an article published by Gould et al (1988).

A limited sleep study generally includes a combination of airflow, thoraco-abdominal movement, oximetry and heart rate measurement (cardiorespiratory sleep study) with some additional measurement of snoring and indirect evidence of episodes of airflow obstruction (American Sleep Disorders Association 1997, Scottish Intercollegiate Guidelines Network 2003). It may be acceptable, particularly in selected patients with a high pretest probability group. If the limited study is negative, a full PSG can still be performed (American Sleep Disorders Association 1997).

Nocturnal pulse oximetry might be used as a screening, or even a diagnostic measure for OSAHS. Douglas et al (1992) demonstrated that oximetry alone could detect 66% of patients with severe OSAHS, but leave the rest with moderately severe OSAHS undiagnosed.

Split-night studies can be used if OSAHS is definitely diagnosed during the first half of the night (an AHI of >40 recorded in the first 2 hrs of PSG). CPAP titration is performed during the second half of the study (American Sleep Disorders Association 1997, Douglas 2002).

1.13 Treatments

Contemporary treatments of OSAHS are directly or indirectly focused on increasing the pharyngeal airway size.

1.13.1 Behavioural or Lifestyle Modifications

Weight loss, avoidance of alcohol, smoking, sedative, sleeping in supine position, and improving sleep hygiene i.e. a regular sleep-wake schedule are the cornerstone of lifestyle modification for patients with OSAHS of any severity (Douglas 2002, Scottish Intercollegiate Guidelines Network 2003, Guilleminault and Abad 2004).

Weight loss and exercise can be beneficial in overweight patients because they increase UA patency and therefore decrease the severity of the disease (Shelton et al 1993, Peppard et al 2000a, Welch et al 2002). Weight loss also may improve the efficacy of other treatments and lower the effective CPAP pressure, and thereby potentially improve compliance.

1.13.2 CPAP/BIPAP Treatment

CPAP is a mechanical device consisting of a flow generator, a flexible air tube and a nasal or oro-nasal mask. The flow generator delivers continuous positive airway pressure into the UA, via a nasal or oro-nasal mask. Its ability to act as a pneumatic splint prevents the passive collapse of the UA due to hypotonia of the pharyngeal muscles during sleep, and leads to symptomatic improvement (Sullivan et al 1981).

Previously CPAP pressure was established under supervision in a hospital-based setting. However, new CPAP technologies now allow for unattended titration of CPAP at home. The most important technological enhancement is auto-CPAP (intelligent CPAP). This system works by detecting UA obstructions (apnoeas, hyopopnoeas, increased air flow resistance or snoring) and adjusting the necessary pressure automatically to the pharyngeal airway to prevent the obstruction (Douglas 2002,

Scottish Intercollegiate Guidelines Network 2003). The aim of the therapeutic titration is to reduce the AHI to less than five. In clinical practice, it is generally accepted that patients with moderate to severe OSAHS and daytime sleepiness should be treated with CPAP (in the absence of surgically correctable anatomical lesions obstructing the UA), but it is less clear whether or not to treat mild OSA in the absence of daytime sleepiness (Engleman 2002a).

CPAP provides significant symptom relief for patients with OSAHS. A recent meta-analysis of CPAP including 12 randomised controlled trials of 738 patients reported that nasal CPAP significantly improves subjective and objective sleepiness across a broad range of sleep-disordered breathing severity (Patel et al 2003, Faccenda et al 2001).

A recent Cochrane review has also assessed 38 randomized trials comparing nocturnal CPAP with inactive control or oral appliances (OAs) in adults with obstructive sleep apnoea (n=1718). In this review, CPAP was found to be effective in reducing symptoms of sleepiness and improving quality of life measures and more effective than OAs in reducing respiratory disturbances in people with moderate and severe OSA. However, most patients preferred the OA to CPAP where both were effective (Giles et al 2006). Although several short term, randomised, double blind, placebo controlled trials have indicated that nCPAP decreases systemic blood pressure (Faccenda et al 2001, Pepperell et al 2002), long-term data are required to show whether CPAP influences the frequency or consequences of other medical conditions associated with OSAHS, such as cerebrovascular disease and cardiopulmonary disease as discussed above (Giles et al 2006).

CPAP compliance, which refers to how long the patient uses CPAP on a nightly basis, is the major limitation of CPAP therapy. McArdle et al (1999) reported that AHI≥30 and ESS>10 at baseline were independent predictors of long-term CPAP use. A randomized controlled trial by Hoy et al (1999) showed that intensive CPAP education and support programs for patient and partner, and additional nights in the sleep facility significantly increased CPAP usage (3.8 to 5.4 hours). Patients with the mild to moderate forms of sleep-disordered breathing, who are not sleepy, often cannot tolerate CPAP treatment, or simply refuse it altogether, due to its cumbersome nature (McArdle et al 1999, Giles et al 2006).

A large number of patients refuse or cannot tolerate CPAP because of its side effects, discomfort and sometimes for psychological reasons. The most often reported side effects are increased nasal congestion and irritation, rhinitis nasal bridge sores, discomfort, claustrophobia, conjunctivitis and noise (Giles et al 2006). Problems may be improved by using chin straps or full face masks, heated humidification and local treatments, such as moisturizers or corticosteroids (Douglas 2002, Scottish Intercollegiate Guidelines Network 2003).

Bilevel systems (e.g., BiPAP) allow independent adjustment to set different pressures for inspiratory and expiratory breaths (Scottish Intercollegiate Guidelines Network 2003) and provide more natural ventilation. However there is no good evidence that bilevel ventilation is useful in OSAHS patients unless there is co-existing obesity hypoventilation syndrome.

1.13.3 Oral Appliances

Oral appliances (OAs) are placed in the mouth during sleep to prevent UA obstruction. OAs function by increasing UA size and preventing the collapse of the tongue and the soft tissue behind the throat and probably act in three ways (1) repositioning the mandible, tongue, soft palate and uvula, (2) stabilizing the mandible, tongue and hyoid bone, and (3) increasing the muscle tone activity of the tongue (Lowe 2000). All appliances fall into two categories: tongue retaining appliances and mandibular repositioning / advancing device (MRS/MAD) which is most commonly used in clinics.

OAs are generally used for patients with primary snoring or mild OSAHS, and are also an alternative treatment for patients with moderate to severe OSAHS who are intolerant of or refuse treatment with nCPAP (American Sleep Disorders Association 1995).
Evidence from randomised controlled trials showed that MRSs can decrease snoring (Stradling et al 1998) and improve day and night time symptoms in patients with mild to moderate OSAHS (Ferguson et al 1997, Mehta et al 2001, Gotsopoulos et al 2002). A recent randomized placebo controlled crossover trial of 61 patients with OSAHS (AHI>10) has also indicated that MRS therapy for over 4 weeks reduces mean 24 hr diastolic blood pressure of 1.8 mmHg (Gotsopoulos et al 2004).

In comparison with CPAP, both MRS and CPAP were effective, but MRSs do not decrease AHI, daytime or nocturnal symptoms as much as CPAP (Ferguson et al 1997, Engleman et al 2002b, Barnes et al 2004). A randomized controlled crossover trial of 114 patients with an AHI of 5-30 using 3 months of treatment with each method—nasal CPAP, MRS, and a placebo—has shown that both CPAP and MRS were more effective than placebo in treating respiratory events, sleep fragmentation, and

hypoxemia, but CPAP was superior to MRS in this regard. Both treatments were more effective in improving quality of life, symptoms, and subjective sleepiness than a placebo. However, MRS was found to be superior to CPAP for nocturnal blood pressure (Barnes et al 2004).

There is no objective method of documenting MRS use – all compliance data are based on self reports which, at least in the case of CPAP use, overestimate actual use (Engleman et al 2002b). The compliance rate with MRS treatment may differ depending on the appliances' design, the particular study and the duration of treatment. A study from our department showed that the reported use was around 50% for patients wearing a simple fixed MRS on an average of 5 hr/night at a median 7 months after fitting (Izci et al 2005). Side effects or lack of efficacy from MRS have been noted to be the main reasons for stopping MRS usage (Ferguson et al 1997, Lowe 2000, Barnes et al 2004, Gotsopoulos et al 2004, Izci et al 2005).

The most common side effects of MRS are initial discomfort, excessive salivation, dryness of the mouth and long-term effects of temporomandibular joint discomfort, possible dental damage, bite change and periodontal disease. (Ferguson et al 1997, Lowe 2000, Mehta et al 2001, Engleman et al 2002b, Izci et al 2005). Recent developments with MRS, specifically the adjustability of mandibular advancement and the ability to titrate may significantly increase their efficacy for optimal treatment (Lowe 2000). Following technical support may increase compliance of OAs.

1.13.4 Surgery

The role of surgery in treating OSAHS is still poorly understood and there is significant disagreement as regards its use as a treatment. This is perhaps ascribable to the fact that there is not a satisfactory number of identified randomized control trail's evaluating surgery for OSAHS. Surgical procedures are attempted to modify the retropalatal pharynx, the retrolingual pharynx, or both (Sher 2002).

Tracheostomy is the first effective surgical procedure for the treatment of OSAHS which is aimed to bypasses the site of upper-airway closure. It is curative with nearly 100% success rate (Partinen and Guilleminault 1990, Thatcher and Maisel 2003), but rarely done due to significant medical and psychological morbidity.

Uvulopalatopharyngoplasty (UPPP) is a commonly performed procedure that enlarges the retropalatal airway by removal of the tonsils along with portions of the anterior and posterior tonsillar pillars and the free margin of the soft palate including the uvula (American Sleep Disorders Association 1996). In a meta-analysis of 37 studies, UPPP decreased significantly the severity of OSAHS as measured by a decrease in the RDI of 38% weighted average (range –72% to +12%). However, less than 50% of patients achieved an apnoea index lower than 10 and its outcome was variable (Sher et al 1996). Furthermore, UPPP has been shown to affect adversely the patient's subsequent ability to use nCPAP (Mortimore et al 1996a). Evidence on long-term follow up after UPPP is poor. Larsson et al (1994) tracked 50 patients for a mean of 46 months after UPPP. Response rates decreased from 60% at 6 months to 30% at 21 months in association with significant weight gain. There is also a lack of evidence regarding which patients will benefit from UPPP (He et al 1988). UPPP is also associated with significant peri-operative mortality and morbidity.

Laser assisted uvulopalatoplasty (LAUP) is an alteration of the UPPP procedure that is in use as a treatment for snoring. A meta-analysis of six case series and one retrospective cohort study containing analysable data revealed an average adjusted-effect size of 0.25, indicating a small reduction in AHI following LAUP. Thus, LAUP is not recommended for the treatment of sleep related breathing disorders by Littner (2001). Ferguson et al (2003) studied 45 patients with mild OSAHS (AHI 10–27 hr) who were allocated to either LAUP or no treatment in the only randomised controlled trial to date. The AHI reduced up to 21% overall and in patient treated by LAUP but AHI did not change in the control group. Twenty-four percent of patients treated by LAUP had a reduction in AHI<10 hr and a satisfactory improvement in symptoms. Despite this limited efficacy, 10 patients (48%) reported significantly improved snoring after the LAUP. The long term results of LAUP need to be studied in controlled studies to avoid "improvements" related to other factors including regression to the mean.

Maxillomandibular advancement osteotomy has been shown to be as effective as CPAP in normalising breathing patterns overnight and improving both symptoms and daytime vigilance in a controlled trial (Conradt et al 1997). Bettega et al (2000) assessed the benefit of a two-step approach in 51 consecutive patients in order to avoid full maxillomandibular advancement. These authors found that limited mandibular osteotomy is not beneficial for most patients with sleep apnoea, while full maxillomandibular advancement decreased AHI significantly from 59 to 11. More data and further information on follow-up decades after this surgery are required. Bariatric surgery may be highly beneficial in the management of morbid obesity and should relieve the symptoms of obese patients with OSAHS. Nasal surgery for the treatment of nasal abnormalities such as a grossly deviated nasal septum or nasal polyposis may

improve snoring and symptoms of OSAHS (Rappai et al 2003) but the effects are often disappointing.

In conclusion, jaw and UA surgeries may be beneficial in selected patients with primary snoring, or mild OSAHS. Their usage is limited due to their cost and the fact that they are invasive and irreversible.

1.13.5 Medications

Pharmacotherapy is a potentially attractive option for treatment of sleep-disordered breathing. As yet there are no drugs which usefully decrease sleep-disordered breathing in patients. In a recent randomized placebo-controlled crossover trial of 10 male patients with moderate to severe OSAHS, intravenous administration of the cholinesterase inhibitor decreased AHI by 21% but also to reduced total sleep time (TST) by 73 min (Hedner et al 2003).

Evidence from two recent randomised placebo controlled trials in patients with OSAHS showed that modafinil, a central nervous system stimulant, may marginally improve alertness (Kingshott et al 2001), and subjective and objective daytime sleepiness (Pack et al 2001). However headache and nervousness are the most common side effects (Pack et al 2001).

These results suggest that the role of pharmacotherapy for sleep-disordered breathing remains controversial. The main systematic review of pharmacotherapy emphasised that most drug treatments used for OSAHS have not been shown to reduce apnoea episodes or improve wellbeing in the long-term (Smith et al 2002).

1.14 Summary

In summary, sleep-disordered breathing is a common condition in the middle-aged adult population that can have serious complications if left undiagnosed and untreated. Sleep-disordered breathing is not only associated with sleep disturbance, but also the more severe forms of OSAHS are associated (independently) with an increased risk of hypertension and cardiovascular morbidity. The impact of sleep-disordered breathing on society, health care and affected individuals is considerable.

CHAPTER 2
UPPER AIRWAY AND PATHOPHYSIOLOGY OF SLEEP-DISORDERED BREATHING

2.1 Introduction

The UA is a very complex structure and plays vital roles for respiratory, digestive and phonatory functions (Remmers et al 1978, Kuna and Remmers 2000). It consists of the nasal airway, the pharynx, the larynx and the trachea (Kuna and Remmers 2000, Ayappa and Rapoport 2003). The pharynx is the main site of airflow obstruction during sleep due to lack of bony and cartilaginous support (Kuna and Remmers 2000, Ayappa and Rapoport 2003). Therefore, the patency of the pharynx is mainly dependent on muscle activity (Kuna and Remmers 2000, Douglas 2002). In this thesis, the main attention will be given to the pharyx, as this is the main site of obstruction and the UA measurements which are taken from this area are central to the thesis.

2.2 The anatomy and physiology of upper airway

The UA is usually divided into four anatomical subsegments (fig. 2.1) (Schwab et al 1995, Kuna and Remmers 2000, Ayappa and Rapoport 2003):

- The nasophranyx lies between the nares and hard palate.
- Velopharynx is the retropalatal space between soft palate and the posterior nasopharyngeal wall, including the uvula and tonsils.
- The oropharnyx is the retroglossal space which extends from the soft palate to the tip of the epiglottis.
- The hypopharynx is located between the base of the tongue and the larynx.

In this thesis, (OPJ – oropharyngeal junction between mouth and the oropharynx), mean cross sectional area from the OPJ to the glottis (CSA.mean; cm^2), and pharyngeal volume (Vp; cm^3) as the integrated area under the curve between the OPJ and the glottis) were chosen as essential measurement points because of their clinical importance and because measurements from these points are reproducible and accurate (Marshall et al 1993a, Martin et al 1995, Martin et al 1997).

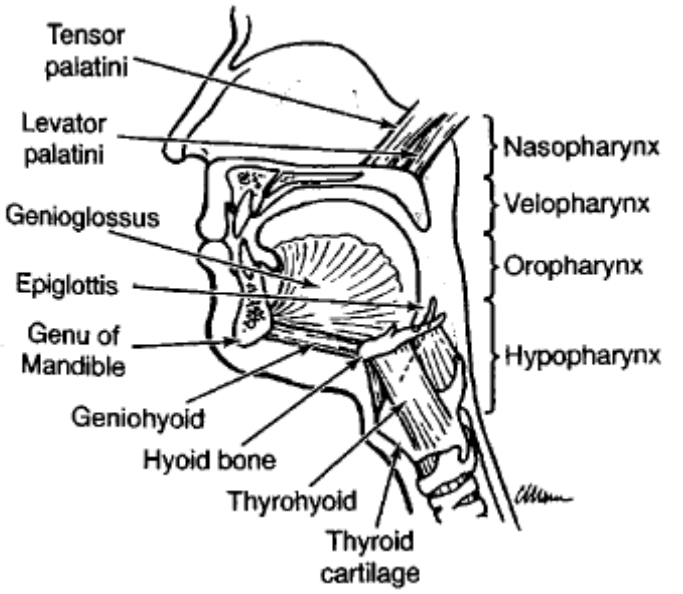


Figure 2.1 The main segments of anatomy of the upper airway showing: nasopharynx, velopharynx, oropharynx and hypopharynx (*From Kuna&Remmers, Principles and Practice of Sleep Medicine, 3rd Edn. 2000; 840-858.*)

2.2.1 Upper airway muscles

There are three main important muscles groups of pharyngeal dilators: the palatal muscles, tongue and hyoid apparatus (fig. 2.1) (Douglas 2002, Fogel 2004).

2.2.1.1 The palatal muscles

In the soft palate there are five striated muscles which are important for respiration. These muscles regulate the position of the soft palate.

●Palatoglossus (anterior tonsillar pillar) lowers the soft palate and raises the tongue (Kuna and Remmers 2000, Douglas 2002).

●Palatopharyngeus (posterior tonsillar pillar) moves the palate downwards and elevates pharynx (Kuna and Remmers 2000, Douglas 2002).

Both of these muscle help to maintain pharyngeal patency during nasal breathing.

●Levator palatine elevates the soft palate, promoting oral respiration. It is tonically active during the whole respiratory cycle (Tangel et al 1995b), but diminishes its activity during sleep (Tangel et al 1995a).

●Tensor palatine tightens the palate from the posterior pharyngeal wall, but tonic activity of the tensor palatini decreases during sleep (Tangel et al 1991).

●Musculus uvulae shortens the palate and contracts the uvula, facilitating oral breathing. It may be involved in nasopharyngeal closure during oral breathing (Douglas 2002).

2.2.1.2 Tongue

The tongue is composed of intrinsic (unattached to bone) and extrinsic muscles (attached to at least one bone). The extrinsic muscles of the tongue include the genioglossus (GG), hypoglossus, chondroglossus and styloglossus. The major extrinsic tongue muscle, GG, protrudes the tongue, retruding, and moving laterally, while other extrinsic muscles retract the tongue (Miller 2002). The frequent phasic activity of GG during inspiration prevents the tongue being passively collapsed into the pharyngeal airway during sleep (Tangel et al 1991). These muscle activities increase in the retroglossal airway in supine normal subjects during wakefulness (Mortimore et al 1999). GG muscle power may weaken with age (Mortimore et al 1999).

2.2.1.3 Hyoid apparatus

The hyoid bone is suspended directly or indirectly from the mandible by ligaments and muscles: infrahyoid muscles (the thyrohyoid, sternohyoid and sternothyroid muscles) and the suprahyoid muscular attachments (the geniohyoid, myelohyoid, hyoglossal, stylohyoid and digastric muscles) (Douglas 2002). These muscles, principally geniohyoid and sternohyoid, control the position of the hyoid bone and stabilize the anterior wall of the hypopharyngeal area (Wiegand et al 1990). The position of the hyoid bone is important to support soft tissue surrounding the UA to maintain UA patency (Tangugsorn et al 2000).

2.2.2 Craniofacial bony structures

The UA is partly enclosed along its length by bony structures, which form a fixed boundary for tissues surrounding the UA including the nasal turbinates, hard palate of the maxilla, mandible, hyoid, and cervical vertebrae (Hudgel and Suratt 1994). The mandible (Rivlin et al 1984) and the hyoid bone (Tangugsorn et al 2000) are the main craniofacial bony structures of UA. The hyoid bone has an exceptional feature in that it does not connect with any other bony or cartilaginous structure.

2.3 Normal upper airway shape and dynamics

In awake healthy subjects, the UA has a longer lateral than anterior posterior dimension (fig 2.2) in supine position as determined by magnetic resonance imaging (MRI) (Schwab et al 1995, Schwab et al 1993b).

Schwab et al (1993b) also studied the dynamic behaviour of the UA with the cine computerized tomography (CT) scanner in normal subjects during wakefulness. There were significant dimensional changes of UA during quiet respiration. They showed that

1) Airway size is larger during expiration than during inspiration.

2) UA cross-sectional area decreases slightly in the early stages of inspiration and widens towards the end of inspiration.

3) UA area increases further, and reaches a maximum size early in expiration and then narrows towards the end of expiration.

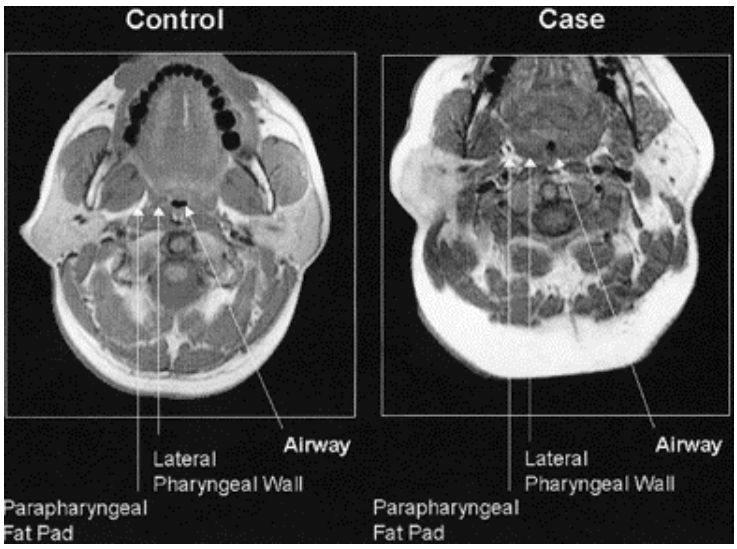


Figure 2.2 MRI of the minimum airway level in the retropalatal region in a normal subject and a patient with sleep apnea. Note that the airway is smaller in the apneic subject than in the normal subject. The lateral pharyngeal walls are larger in the apneic subject than in the normal subject (*From Schwab Am J Respir Crit Care Med 2003; 168: 522–30*)

2.4 UA Patency and contributing Factors

There is a dynamic interaction between anatomy, pharyngeal muscle activity and neuromuscular control which maintains pharyngeal airway patency. Any factor disturbing this interaction could cause UA obstruction.

2.4.1 Pharyngeal dilator muscle activation

UA patency vitally depends on dilator muscles activity (Drummond 2002). At inspiration pharyngeal pressure created by the inflation of the lungs is likely to suck the

UA closed. The activity of the UA dilating muscles which is increased during inspiration offset the collapsing influence of negative airway pressure (Fouke et al 1986, Kuna and Remmers 2000, Mortimore and Douglas 1997, Mortimore et al 1995). The muscles which are active during inspiration with less activity during expiration are called inspiratory phasic UA muscles including palatoglossus, palatopharyngeus, genioglossus and geniohyoid. Genioglossus activity is pivotal to the control of the pharynx (Tangel et al 1991).

The other muscles group in pharynx is called the tonic or postural muscles such as the tensor palatine and levator palatine (Tangel et al 1991, Fogel 2004). These muscles contract slowly and maintain a relatively constant level of activity, thereby promoting pharyngeal patency. When this postural drive is lost during sleep a pharyngeal resistance may increase (Tangel et al 1991, Tangel et al 1995a, Tangel et al 1995b).

The mechanisms controlling pharyngeal muscle activation are also important for UA patency. Several mechanisms are involved both functionally and anatomically such as direct input from the brainstem respiratory central pattern generator (Bianchi et al. 1995), chemoreceptive inputs (Onal et al 1981), 'wakefulness' drive (Fogel et al 2003c) and the influence of lung volume on pharyngeal patency (Van de Graaff 1988, Deegan and McNicholas 1995). The importance of each factor may differ from one person to another.

2.4.1.1 Respiratory neuromuscular control of pharyngeal muscles

The inspiratory phasic and tonic muscles likely receive their motor output from groups of neurones within the brainstem that have different firing patterns relative to the

respiratory cycle. The hypoglossus motor system within the medulla supplies motor output to both the intrinsic and extrinsic tongue muscles. The medial branch of the hypoglossus nerve stimulates GG and geniohyoid (the tongue protrudors) and the lateral branch of the hypoglossus innervates styloglossus and hyoglossus (the tongue retractors). The pharyngeal branch of the vagus stimulates the pharyngeal constrictor muscles. The glossopharyngeal nerve gives motor output to the stylopharyngeus muscle (Kuna 2001). The neurotransmitters norepinephrine and serotonin also have tonic excitatory influences upon the hypoglossal motor neurons increasing muscle activity (Fogel et al 2003a). However, during general anaesthesia the central component of this control is reduced (Drummond 2002) so that the activity of UA muscles is lost.

The pharyngeal inspiratory phasic muscles are known to work 50-100 ms earlier than diaphragmatic activity. As a result of this pre-activation, the UA is enlarged and stabilized as the intraluminal pressure becomes increasingly subatmospheric (Strohl et al 1980). The presence of this pre-activation supports the presence of pre-motor inputs to the hypoglossal motor nucleus which receives direct input from central pattern generating neurons in the brainstem (Bianchi et al. 1995).

In healthy individuals, there is a precise coordination between neural activity and the activation of the pharyngeal muscles which functions to meet the physical demands of the UA. Any problems occurring with this system could thus contribute to UA collapse.

2.4.1.2 'Wakefulness' drive

The effect of 'Wakefulness' drive on the UA muscles has been described (Fogel et al 2003c). Fogel et al (2003c) investigated the effect of sleep onset (transition EEG activity

from wakefulness to sleep) on ventilation, UA muscle activation and UA resistance in healthy men. Subjects were studied on nasal CPAP (to remove a negative pressure stimulus to muscle activation) on one of the two nights (order randomized). Initially, 5–10 min of data was recorded during quiet breathing in order to estimate the level of GG-EMG and TP-EMG. They found that tone in both GG-EMG and TP-EMG was reduced by the application of nasal CPAP during wakefulness, but CPAP application did not change the decrement in either UA muscles' EMGs in the first two breaths at sleep onset-transition. In the third to fifth breaths following transition, there was subsequent recruitment of muscle activity, such that GG-EMG (not TP-EMG) activity recovered to a stable level. The reduction in GG-EMG seen immediately at the transition in both control and CPAP nights suggests that this is possibly due to the removal of a separate intrinsic wakefulness drive to this muscle. A further study by the same group confirmed a number of these findings (Fogel et al 2005).

2.4.1.3 The negative-pressure reflex

Substantial evidence in animal (Mathew 1984) and human (Akahoshi et al 2001; Fogel et al. 2001; Malhotra et al. 2002b) supports that negative pressure is the most important local stimulus to activation of the pharyngeal muscles during wakefulness. The application of negative pressure to the UA leads to an immediate and robust activation in UA dilator muscles, including GG (Malhotra et al 2000b, Berry et al 2003, Malhotra et al. 2002b), palatoglossus (Mathur et al 1995), palatopharyngeus (Mortimore and Douglas 1996b), levator palatini (Mortimore and Douglas 1997) and the tensor palatini muscles (Wheatley et al 1993b).

The latency of this response from the time of application of the stimulus (generally within 100 msec) suggests that it is a neural reflex (Wheatley et al 1993a, Mortimore et al 1995). Topical anaesthesia of the UA and non-rapid eye movement (NREM) sleep may delay this reflex but does not completely eliminate the response to negative transmural pressure (Wheatley et al 1993a, Fogel et al 2000).

Malhotra et al (2000a) measured pharyngeal dilator muscle activation in the presence and absence of UA respiratory stimuli in five OSA patients, mean aged 51, who had been previously tracheostomized for treatment of OSA (AHI >50 per hour of sleep prior to tracheostomy). Patients wore a nasal mask connected to a two-way valve partitioning inspiration and expiration. Each patient was studied under the two conditions of nasal (breathing exclusively through the nose) and tracheal breathing (the stoma was opened and the vast majority of flow occurred through the stoma). Negative-pressure (from −8 to −14 cm H_2O pressure) was applied through the nasal mask during both nasal and tracheal breathing and the GG-EMG was recorded with two stainless steel, Teflon-coated, 30-gauge wire electrodes. All five study patients showed an attenuated negative-pressure reflex and increased collapsibility (measured by the pressure decrement between the choanae and epiglottis during negative-pressure pulses) when ventilation was switched from nasal breathing to breathing through the tracheostomy. These findings suggest that absence of upper airway stimuli immediately reduces upper airway dilator muscle activity in awake patients with obstructive sleep apnoea.

Akahoshi et al (2001) studied 19 awake healthy adults using an iron lung which decreases spontaneous respiratory effort. There remained a linear relationship between

the negative pressure in the airway and GG-EMG activation. This was influenced by changes in PO_2, PCO_2 or airflow. Thus, even in diminished (or absent) central drive to the respiratory pump muscles, UA muscles can response rapidly to collapsing negative pressure. These results support the idea that UA receptors, which possibly responsive to negative pressure, are important in driving the augmented GG activation to maintain airway patency. These suggest an association between airway pressure and pharyngeal dilator muscle activity.

2.4.1.4 Chemoreceptive inputs

Changes in blood gas tensions due to obstructive events activate chemoreceptors leading to activation of the UA dilating muscles and hypoglossal motor nerve output (Onal et al 1981). However studies showed that chemoreceptor stimuli alone does not induce pharyngeal dilator muscle activation.

In a recent study Pillar et al (2000b) measured ventilation, airway resistance, GG and tensor palatini EMG, plus end-tidal PCO_2 ($PETCO_2$) in 18 healthy subjects during wakefulness, stage 2 and slow-wave sleep and demonstrated that despite increment in ventilation, hypercapnia failed to activate pharyngeal dilator muscles during NREM sleep. The authors concluded that chemoreceptor-induced pharyngeal dilator muscle activation alone is unlikely to explain the paucity of sleep-disordered breathing events during NREM.

Stanchina et al (2002) examined the responsiveness of GG-EMG to chemical and mechanical stimuli during NREM sleep in healthy individuals. GG-EMG was measured under basal conditions and during hypoxia, hypercapnia, and inspiratory resistive loading. The results demonstrated that the GG muscle was less responsive to either

chemical stimuli (hypercapnia, hypoxia) or inspiratory resistive load alone during NREM sleep, but the combination of hypercapnia and resistive loading activated the GG muscle. Thus, the interaction between mechanoreceptive and chemoreceptive can be more effective on UA muscle activity than either of them acting alone.

2.4.2 Mechanical factors affecting upper airway patency

2.4.2.1 Lung volume

Lung-volume changes may also influence UA size and pharyngeal resistance by affecting pharyngeal muscle function and, thus, may influence pharyngeal patency in both human and animals (Van de Graaff 1988, Van de Graaff 1991, Stanchina et al 2003). Stanchina et al (2003) investigated the effects of isolated lung-volume changes on pharyngeal collapsibility and mechanics and GG muscle activation during stable NREM sleep in 19 healthy subjects (mean age: 30, mean BMI: 24.5 kg/m2) at baseline, increased end-expiratory lung volume and decreased end-expiratory lung volume. They found that reduced lung volumes led to increased inspiratory airflow resistance and increased GG-muscle activation compared to baseline and that the pharynx was more collapsible at low lung volumes.

This direct relationship between lung volume and UA patency may be due to longitudinal traction created on mediastinal and UA structures (Van de Graaff 1988). Caudal traction may transmit thoracic subatmospheric pressure through the trachea and pharynx (Van de Graaff 1988). During this event, increased "tracheal tug (caudal movement of these structures)" leads to an increase in UA size (Van de Graaff 1991), probably by causing pharyngeal unfolding or decreased pharyngeal compliance by

stretching UA tissues. Additionally it may stabilize the UA by changing the position of structures such as the hyoid (Fogel et al 2003a).

The collapsibility of the airway increases as lung volume decreases as a result of changes in posture from upright to the supine position, or transitions from wakefulness to sleep especially in obese patients with OSAHS (Hoffstein et al 1984, Fogel et al 2003a).

2.4.2.2 Position and Gravity

Body position is an important determinant of UA calibre (Douglas et al 1993). Sleeping in supine position, when gravity is negatively influencing the width of the UA, increases the collapsibility of the UA by dorsal movement of the tongue and soft palate into the pharyngeal airway (Fouke and Strohl 1987, Deegan and McNicholas 1996). It has also been shown that the change from the upright to supine position reduces the pharyngeal cross sectional area in most normal subjects during wakefulness, perhaps due to increased tissue pressure around the UA (Fouke and Strohl 1987).

Isono et al (2002) showed that lateral position improves maintenance of the passive UA patency in patients with OSAHS by increasing maximum cross sectional area and decreasing the closing pressure at both retropalatal and retroglossal airways.

As well as body position, the position of the head and neck may affect UA patency due to anatomic and mechanical changes in UA. While neck extension decreases compliance of the oropharyngeal airway wall, neck flexion and bite opening increase UA resistance decreasing maximum cross sectional area, which is likely to promote UA instability (Isono et al 2004).

2.4.2.3 Breathing route

The breathing route also affects the UA muscle activities (Douglas et al 1993). The activities of the palatoglossus (Mathur et al 1995) and the palatopharyngeus (Mortimore and Douglas 1996b) during nasal breathing increase in supine position and work against the effects of gravity on the soft palate and tongue. Douglas et al (1993) also showed that the patients with OSAHS have higher and the normal subjects lower EMG tone with nasal breathing in comparison with oral breathing on both inspiration and expiration. This study suggests that both body posture and breathing route are important determinants of UA muscle tone. Fitzpatrick et al (2003) reported that UA resistance and the propensity to UA collapse during sleep are significantly less during nasal breathing than oral breathing in a crossover study which compared UA resistance during sleep in nasal and oral breathing in healthy subjects. This mechanical advantage may account for the high prevalence of nasal breathing during sleep in normal subjects.

2.4.2.4 Surface adhesive

Surface adhesive forces and fluid elasticity of the mucosa may affect UA patency. Lowering the surface tension of UA lining liquid can decrease both UA collapsibility and the severity of sleep-disordered breathing (Kirkness et al 2003).

2.4.2.5 The vascular tone of the blood vessels

It has been demonstrated that vasoconstriction decreases the airway area and vasodilatation increases UA resistance (Wasicko et al 1990), thus affecting UA patency.

In summary these results suggest that UA patency cannot be attributed only to the activity of UA muscles. Anatomical and mechanical factors affecting UA muscles also have an influence upon UA patency.

2.5 Gender differences as regards upper airway

There is no consistent gender difference in the pharyngeal cross-sectional area. A number of studies have shown that healthy women have a smaller airway calibre than healthy men; this has been shown using the acoustic reflection technique (Martin 1997, Huang et al 1998, Kamal 2002). Martin et al (1997), showed that men had larger UAs than women when seated but a similar UA caliber supine, and that men had a larger percentage UA narrowing upon lying down. However radiological imaging studies have failed to show such a difference (Schwab 1993a, Whittle et al 1999).

There is consistent evidence of a gender difference in the pharyngeal airway length. Malhotra et al (2002) revealed using MRI scanning that men had substantially longer pharyngeal airway lengths than women even when length was normalized for body height. There was also an increased cross-sectional area of the soft palate (Malhotra et al 2002, Whittle et al 1999) and an increased airway volume in men compared with women (Malhotra et al 2002). These observed gender-related differences in pharyngeal anatomy may have an important impact on the vulnerability of the UA to collapse.

Regarding UA muscle activities, Popovic and White (1995) reported that healthy women had a higher level of GG muscle activity during quiet breathing in wakefulness than men, but later studies failed to obtain the same finding (Pillar et al 2000a, Jordan et al 2002, Malhotra et al 2002). O'Connor et al (2000) analysed gender differences in the polysomnographic features of OSAHS in a retrospective study of 830 patients. They

found that although during NREM sleep women had a lower AHI than men, during REM sleep women and men had a similar AHI. These suggest that the loss in muscle tone in REM sleep leaves women's UA as vulnerable as men's to airway obstruction.

The pharyngeal compliance was greater in males than in females (with posture changes) (Martin et al 1997, Huang et al 1998). However, these structural and functional differences were less distinguishable when investigated in the supine posture, compared with in the erect posture using acousic reflectometry (Huang et al 1998, Martin et al 1997). On the other hand, Jordan et al (2005) studied 12 men and 12 women who were matched for BMI during stable supine NREM sleep. When AHI matched, women had a higher BMI than men, but pharyngeal collapsibility was similar between men and women. In the BMI-matched subgroup, women had less severe OSA during NREM sleep. These results suggest that women may be protected from developing sleep-disordered breathing by having a less collapsible UA for any given degree of obesity.

Deegan and McNicholas (1996) reported that in male patients with OSA, abdominal girth correlated more with AHI than with neck circumference and BMI. On the contrary, in female patients with OSA neck circumference was the best correlate of AHI. This suggests a possible sex difference in fat distribution and its effect on AHI.

In a community based study of 15 men and 15 women without sleep-disordered breathing, using UA imaging Rowley et al (2002) measured UA cross-sectional area and retropalatal compliance in wakefulness and NREM sleep. They showed that retropalatal compliance tended to be higher in men during both wakefulness and NREM sleep. However, compliance was similar in men and women after adjustment for neck

circumference. The authors concluded that differences in neck circumference between the genders can account for the gender difference in retropalatal compliance.

The data regarding airway resistance and collapsibility are conflicting between genders. Trinder et al (1997) reported that healthy men had a greater UA resistance during NREM sleep compared with women. However, Thurnheer et al (2001) reported that there were no major age or gender differences regarding airway resistance during sleep in healthy subjects. Pillar and colleagues (2000a) also reported that men had larger increases in UA resistance and more flow limitation than age and BMI-matched women during inspiratory resistive load application.

There are contradictory data and concepts concerning the effect of female sex hormones on the UA during sleep. Some evidence supported the idea that female sex hormones may provide a protective effect on the UA (Popovic and White 1998, Shahar et al 2003). On the other hand, the hormonal changes which occur with pregnancy, predominantly in the third trimester may increase the propensity to sleep-disordered breathing due to affecting ventilatory control and the UA dynamics (Kowall et al 1989, Lefcourt and Rodis 1996, Edwards et al 2002). In the third chapter this issue is detailed. Evidence regarding the effect of hormone replacement treatment is also variable. In most clinical trials, hormone replacement therapy, at least in the short term, has shown small improvement or no change in the frequency of sleep-disordered breathing in postmenopausal women (Cistulli et al 1994a, Saaresranta et al 2003, Bixler 2001, Polo-Kantola et al 2003, Shahar 2003).

As far as male sex hormones are concerned, the direct effects of these hormones on sleep apnoea severity appear minimal. Short-term administration of high-dose testosterone has been demonstrated to shorten sleep and worsen sleep apnoea in older men (Liu et al 2003). In a study of 11 hypogonadal men during sleep both on and off testosterone-replacement therapy, AHI increased significantly during testosterone replacement from 6.4 to 15.4. per hour of sleep (Schneider et al 1986). Thus, testosterone may aggravate sleep-disordered breathing due to a concomitant rise in collapsibility (Cistulli et al 1994b). However, androgen blockage did not have any obvious effect on UA (Stewart et al 1992).

In summary, although women have a smaller airway calibre than men; they may have a less collapsible UA for any given degree of obesity and less severe OSA during NREM sleep compared with the BMI-matched men. These gender differences in the UA may occur as a result of sex hormones. However, evidence concerning the effect of female sex hormones is contradictory. The effects of male hormones on UA have been found to be minimal.

2.6 The balance of forces

The patency of the pharynx during inspiration depends on the balance between dilating and collapsing forces, as explained in the balance of forces model. According to this model, airway dilating forces are generated by pharyngeal muscles and collapsing forces are generated by subatmospheric (negative) intraluminal pressure (Pi) in the pharyngeal airway transmitted from the thorax to pharynx during inspiration and extraluminal pressure or tissues pressure (Pti) around the airway (Remmers et al 1978, Brouillette and Thach 1979, Kuna and Remmers 2000). The dilator muscles work to counteract both

these collapsing pressures (Isono and Remmers 1994, Kuna and Remmers 2000). In normal subjects, the pressure required to collapse the UA in the absence of UA muscle activity (i.e. the closing pressure) is subatmospheric. In a potentially collapsible UA, positive pressures are required to maintain the patency of the UA during sleep (passive UA). This balance of forces could prevent the UA from progressing from partial to complete obstruction (Deegan and McNicholas 1995).

2.7 Upper airway compliance and collapsibility

UA compliance may be described as the potential of the airway wall to collapse. According to the Starling resistor model, a normal human UA acts as a collapsible tube during sleep (Schwartz et al 1988, Smith et al 1988). Intraluminal negative (suction) pressure applied to the downstream end of this collapsible tube during each inspiration can increase the flow only to a limited extent due to the negative pressure decreasing UA size. The flow mechanism depends essentially on the size and the dynamic behaviour of the collapsible section between soft palate and hypopharynx (Isono et al 1997). UA narrowing increases the gas velocity and decreases the lateral pressure which will cause a further reduction in UA size (Bernoulli effect) (Brouillette and Thach 1979). Thus the air flows through the pharynx only when the upstream pressure exceeds a critical pressure (Isono et al 1997).

Although many methods have been used to measure UA collapsibility, the most applicable method in humans is the pharyngeal critical pressure (Pcrit -an index of pharyngeal collapsibility), which was developed from the relationship between maximal inspiratory airflow and nasal pressure (Schwartz et al 1988, Schneider et al 2002). The nasal pressure at which the extrapolated flow reaches zero is the critical closing pressure

(Schneider et al 2002). Positive values of Pcrit differentiate patients with OSAHS from snorers and normal subjects (characterized by a negative Pcrit) and Pcrit is related to the severity of the sleep-disordered breathing (Gleadhill et al 1991). Patients with sleep-disordered breathing (especially a severe form of sleep-disordered breathing, OSAHS) have more positive pharyngeal Pcrits, which reflects the increased UA collapsibility. This increased collapsibility predisposes to pharyngeal collapse.

2.8 The effect of sleep on the normal upper airway and ventilation

The transition from wake to sleep is associated with alteration in UA muscle activity in healthy individuals. These changes may explain why sleep is associated with a significant increase in UA resistance in healthy individuals. However, studies on the effect of sleep on pharyngeal muscle activation are contradictory. Some studies showed a reduction in both tonic and phasic tone during the sleep in the geniohyoid (Wiegand et al 1990), tensor palatini (Tangel et al 1991, Mezzanotte et al 1996), levator palatini and palatoglossus (Tangel et al 1995a, Pillar et al 2000b). In contrast to these findings, other studies demonstrated that in normal individuals the reduction in GG-EMG occurs immediately at sleep onset (Mezzanotte et al 1996), but that it recovers to a stable level during NREM sleep (Tangel 1991, Worsnop et al. 1998, 2000, Pillar et al 2000b, Fogel et al 2003c, Fogel et al 2003b). However, studies of the GG have been unable to clearly demonstrate whether the recovery of GG-EMG during NREM sleep in normal individuals result from local activation of the muscle such as negative pressure or from central pattern-generating neurons. Diaphragmatic EMG was also reported to recover to baseline levels after an immediate decrease at sleep onset (Worsnop et al. 1998, Fogel et al 2003b). On the other hand, responses of the GG to negative pressure, added loads (inspiratory resistive loading) and elevated CO_2 levels are substantially reduced during

NREM sleep and further during REM sleep (Wiegand et al 1988, Wheatley et al 1993a, Wheatley et al 1993b, Horner et al 1994, Malhotra et al. 2000b).

Another important respiratory event during sleep is the experience of a decreased response to an increase in the work or load of breathing (resistive loading), although the ventilatory control system's capacity to compensate for this is necessary for the preservation of chemoreceptor homeostasis. As a result of this, decrements in tidal volume, minute ventilation, and alveolar hypoventilation (with ensuing elevation of arterial $PaCO_2$) occur after load application (Wiegand et al 1988, Malhotra et al 2001). Malhotra et al (2001) recently conducted a study evaluating two collapsibility-measurement techniques (negative pressure pulses and inspiratory resistive loading) in normal (total n=22) and apnoeic subjects (n=38) during wakefulness and sleep. Their findings showed (1) a significant correlation between these two measures of collapsibility, and (2) a significant increase in pharyngeal collapsibility during sleep as compared to wakefulness. Both controls and apnoeics had a significant increase in pharyngeal collapsibility during sleep as compared to wakefulness but apnoeics had significantly greater pharyngeal collapsibility than controls while awake.

In addition to sleep-related changes in UA muscles, local anesthesia has also been shown to induce UA obstruction during sleep in healthy individuals (McNicholas et al 1987). Use of alcohol and sedatives before bedtime can relax the musculature in the UA, which obstructs breathing in healthy individuals. Sleep deprivation has also been reported to decrease the activity of the GG muscle in response to increased CO_2 in healthy individuals (Leiter et al 1985).

2.9 Size and shape of pharyngeal airway in patients with sleep-disordered breathing

Many studies using multiple techniques including acoustic reflection, cephalometry CT scanning or MRI have shown that patients who are habitual snorers with or without OSAHS have small pharyngeal airway sizes and potentially a more compliant or collapsible airway compared to normals (Rivlin et al 1984, Bradley et al 1986, Schwab et al 1993a, Ferguson et al 1995, Martin et al 1995, Schwab et al 1995, Isono et al 1997, Mortimore et al 1998). The variability in airway size is determined by the relationship between the fixed dimensions of the craniofacial skeleton and the volume and distribution of soft-tissue structures especially adipose tissue.

It has been also shown that snorers and sleep apnoeic patients have a pharynx in a circular or elliptic shape with the long axis oriented in the antero-posterior direction (lateral narrowing) (fig. 2.2) (Schwab et al 1993a, Schwab et al 1995, Schwab et al 2003). Leiter (1996) has postulated that this disorientation of the airway shape may decrease pharyngeal dilator muscles' ability to maintain pharyngeal patency influencing the mechanical effectiveness of UA muscle contraction.

2.10 Pharyngeal airway during sleep in patients with sleep-disordered breathing

In patients with sleep-disordered breathing, there is no significant UA impairment during wakefulness. Dilator muscles are able to respond to changing conditions and maintain UA patency in the face of negative intraluminal pressures during inspiration. In fact several studies showed that GG and tensor palatine EMG were greater in patients with OSAHS than normal subjects (Mezzanotte et al 1992, Fogel et al 2001). However,

a progressive loss of UA muscle tone during sleep leaves the pharynx vulnerable to negative collapsing pressures during inspiration, especially in the patients with already narrow airways (Remmers et al 1978, Deegan and McNicholas 1995).

The neuromuscular reflex mechanism involved in activating UA dilators in response to negative pressure is also lost or seriously attenuated at sleep onset in the pharyngeal airway together with a decreased muscle activity (Mezzanotte et al 1996, Fogel et al 2005, Wheatley et al 1993a, Horner et al 1994, Malhotra et al 2000b). Thus, palatal muscle reflex activity in response to UA negative pressure has been reduced in OSAHS patients compared with normal subjects (Mortimore and Douglas 1997). However, a significant improvement has been reported in patients' EMG response to negative pressure after 2 weeks of CPAP treatment (Mortimore and Douglas 1997).

Furthermore, immediate ventilatory compensation for additional inspiratory load (resistive loading) is impaired more in OSAHS patients compared to normal subjects during sleep (Malhotra et al 2001).

In snorers, pharyngeal compliance increases during sleep with the occurrence of inspiratory flow limitation as flow plateaus during inspiration (Guilleminault et al 1993, Edwards et al 2000b). Gold et al (2002) have compared UA collapsibility between normal subjects, patients with UARS, and patients with OSAHS using the Starling resistor model of the UA during sleep. Comparisons of both Pcrit values and Ptherapeutic (determination of therapeutic level of nasal CPAP) values demonstrate that the inspiratory flow limitation of patients with UARS is associated with UA collapsibility which lies between that of normal subjects and patients with mild-to-moderate OSAHS.

Airway obstruction in patients with OSAHS can lead to transient lung abnormalities which may worsen gas exchange (Drummond 2002). A decrease in lung volume at sleep onset may also cause UA collapsibility in patients with OSAHS (Fogel et al 2003a), but this does not occur in either non-snorers or simple snorers (Hoffstein et al 1984, Bradley et al 1986, Worsnop et al 1998).

Sleep deprivation (Leiter et al 1985), fragmentation (Series et al 1994), neck flexion and bite opening of the passive pharynx in patients with sleep-disordered breathing (Isono et al 2004) may affect UA muscle activity and thus contribute to UA collapsibility.

2.11 Mechanism of upper airway narrowing in patients with sleep-disordered breathing during sleep

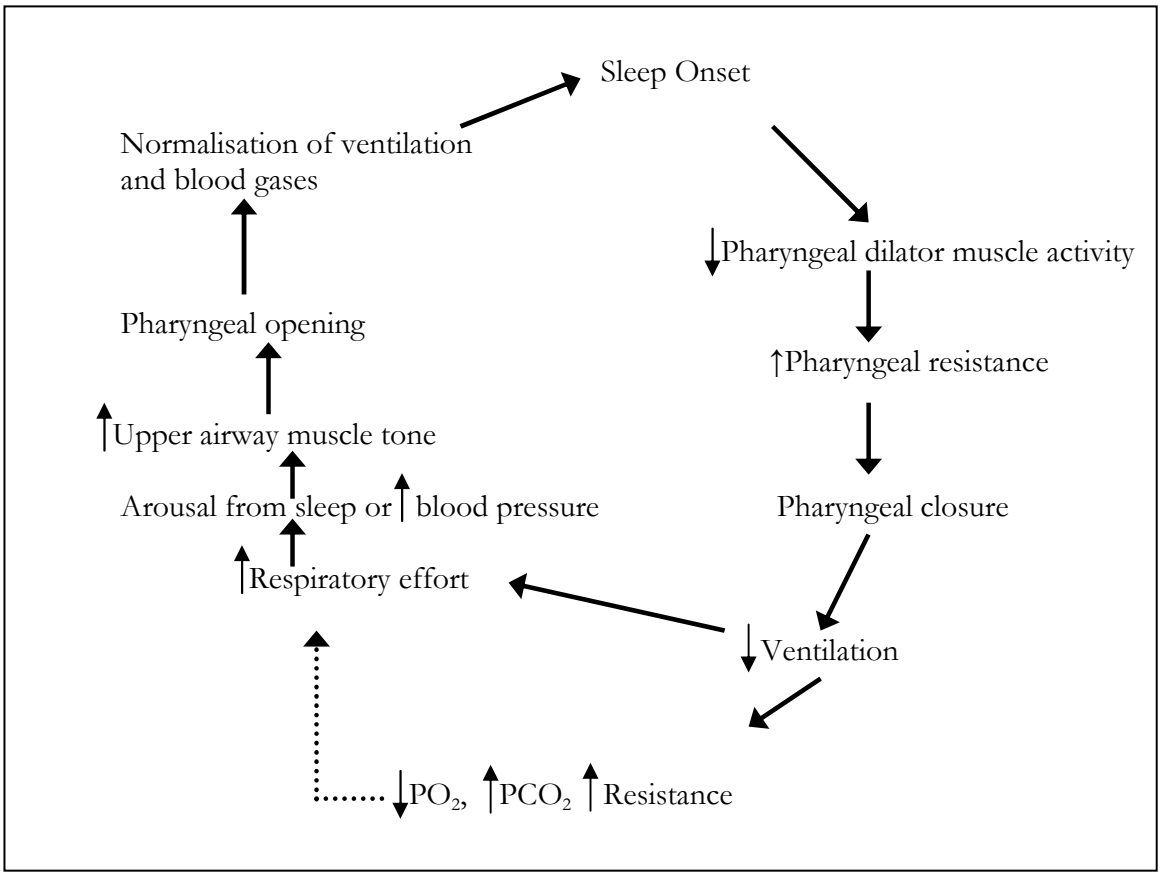
A combination of an anatomically small airway, hypotonia in striated muscles of UA, reduced reflex mechanisms in the UA by sleep and inadequate resistive load compensation during sleep may weaken the ability of the UA to protect itself from suction collapse by negative pressures created during inspiration. Thus, a complete or partial UA collapse can occur in patients with OSA during sleep.

This obstructive respiratory event (figure 2.3) continues with each inspiratory effort until the levels of intrathoracic pressure reach a critical level which seems to stimulate arousal. The brief arousal restores UA patency and decreases CO_2 tension and creates better O_2 saturation. In severe forms of sleep-disordered breathing after a few unobstructed breaths, obstruction recurs again. This cycle repeats with sleep onset and may recur hundreds of times in the night. Although arousal from sleep is considered to be an important mechanism for re-establishing airway patency, arousals may decrease

respiratory drive associated with the hypocapnia which results from post-apnoeic hyperventilation (Berry and Gleeson 1997) and likely increase the severity of the disorder by promoting greater ventilatory instability (Younes 2004).

Multiple arousals result in sleep fragmentations which impair patients' daytime functioning (Martin et al 1996) and transient surges in blood pressure (Lofaso et al 1998, Stradling et al 2000). Additionally, in some cases, respiratory efforts during sleep terminate with blood pressure rise rather than visible EEG arousal (Davies et al 1993).

Figure 2.3. Schematic diagram of pathophysiologic event of upper airway closure during sleep. *Modified from Kingshott, Factors Affecting daytime Function in the Sleep Apnoea/Hypopnoea syndrome. Unpublished PhD thesis. 1998; p7.*



2.12 Site of obstruction in upper airway

The most common sites of obstruction are the retropalatal (in almost 100% at the retropalatal airway) and retroglossal regions (in 50% of the patients at the level of oropharynx) (Schwab et al 1993a, Schwab et al 1995, Isono et al 1997, Isono et al 2003, Schwab et al 2003). Obstruction may also occur in the hypopharyngeal airway (Hudgel 1986).

The site of UA narrowing during wakefulness does not necessarily correlate with the site of obstruction during sleep. Trudo et al (1998) performed a study with 15 normal subjects using MRI during wakefulness and sleep and found that the mean minimal cross sectional area was decreased by 28% in the retropalatal and by 22% in the retroglossal region during sleep as compared with values in anatomically matched axial images during wakefulness. Airway anteroposterior and lateral dimensions were also significantly reduced in the retropalatal region during sleep. Therefore UA resistance may increase in normal subjects during sleep (Tangel et al 1991, Mezzanotte et al 1996, fogel et al 2003b) with a further increase in habitual snorers (Tsushima et al 1996).

Tsushima et al (1996) reported (using digital fluoroscopy) that the UA was more collapsible and smaller at the level of velopharynx in snorers compared with non-snoring controls during wakefulness. Retropalatal airway narrowing was also observed during sleep in normal subjects (Wheatley et al 1993b).

These findings suggest that the site of obstruction not only varies between individuals but also that the same individual may have multiple sites of obstruction, that is, seesawing obstructions which are mainly at the level of the oropharynx (Remmers et al

1978). The site of obstruction also may differ, being at one site during wakefulness and another at the onset of sleep (Hudgel 1986).

2.13 Methods to identify the sites of upper airway obstruction

Several methods have been used to localize the obstructed area of the UA in patients with sleep-disordered breathing. These methods include physical examination, physiologic measurement of pressure and resistance along the UA which can be assessed by external mass-loading of the abdomen or chest, or by artificially increasing the airway resistance at the mouth (Wiegand et al 1988, Malhotra et al 2001).

In addition to these methods, imaging techniques have been used including fiberoptic endoscopy (with the so-called Muller maneuver), cephalometric roentgenograms, fluoroscopy, CT, and MRI (Shepard t al 1991). However, some of these techniques are invasive, require exposure to radiation, or are expensive.

Full assessment of the UA requires the use of dynamic techniques as the calibre of the UA changes with respiratory phase, body position, and lung volume, for example. Acoustic reflectometry is noninvasive, accurate, and reproducible, and provides an objective measurement of the UA dimensions (Marshall et al 1993a). It does not require radiation exposure, is quick and inexpensive to perform and as a result, easily repeatable and can be used with subjects in all postures. It requires patient cooperation, but it results in a high patient acceptance. We have used this technique because of these features, accepting that it has the major limitations that measurements have to be made via the oral route and that it cannot be used during sleep. Detailed information about acoustic reflectometry is provided in chapter 4.

2.14 Factors causing upper airway obstruction in patients with sleep-disordered breathing

2.14.1 Skeletal factors

Retroposition of the mandible and maxilla (Ferguson et al 1995) leads to antero-posterior narrowing of the pharynx due to posterior displacement of the soft palate and tongue (Ferguson et al 1995). Sforza et al (2000) reported that the position of the hyoid bone and the distance between the hyoid bone and the mandibular plane were correlated with Pcrit in a group of 57 men with OSAHS. Verin et al showed that the posterior airway space and the distance from hyoid bone to mandibular plane and to pharyngeal posterior wall predict UAs resistance in awake apnoeic patients and controls (Verin et al 2002). Retrognathic facial structures might be a risk factor for UA narrowing and obstructive sleep apnoea in infants. Rees et al (1998) examined facial bone structure in 15 infants who had died of the sudden infant death syndrome (SIDS) and 15 aged matched controls. Maxillary and mandibular positions were measured using cephalographs. Infants dying of SIDS had significantly smaller maxillary angles than controls. Mathur and Douglas (1994) asked 38 OSAHS relatives and 38 controls matched for age, sex, height, and weight to complete a questionnaire enquiring "were there any unexpected infant deaths under one year of age" and about the cause of death, if known. There was an increased family history of SIDS in adults with OSAHS. Gunn et al (2000) performed respiration-timed UA radiographic measurements in 21 asymptomatic neonates with clinical micrognathia and compared their radiographic measurements with those of a previously reported cohort of 35 normal infants. They followed up micrognathic infants and 27 normal infants referred for parental anxiety due to the death of a previous infant from SIDS for 6 months on home apnoea monitors, and found that infants with micrognathia had smaller UAs than normal

infants in the neonatal period. These findings suggest that the retroposition of the maxilla and micrognathia were common features in families who had both the OSAHS and SIDS. Patients with mild to severe OSAHS benefit from mandibular advancements (appliances or surgery) due to increasing the size of the pharyngeal area and reducing the Pcrit (Tsuiki et al 2004, Rachmiel et al 2005).

2.14.2 Soft tissue factors

The soft tissues of the pharynx including the tonsils, soft palate, uvula, tongue, and the lateral pharyngeal walls in the adult are important in influencing airway size (Schwab et al 1993b, Deegan and McNicholas 1995, Schwab et al 1995, Schellenberg et al 2000, Schwab et al 2003). Enlarged tonsils and adenoids also may lead to UA narrowing in children. Surgical correction of these anatomic defects can increase UA size and decrease sleep-disordered breathing.

Schwab et al (2003) found that the volume of tongue, soft palate, lateral pharyngeal walls, and parapharyngeal fat pads was significantly greater in subjects with sleep apnoea compared with control subjects using a three-dimensional volumetric approach. They also found that the greatest odds ratios for the development of sleep apnoea were associated with increased volume of the lateral pharyngeal walls, tongue, and total soft tissue after adjusting for sex, ethnicity, age, craniofacial size, and visceral fat in the neck. Other UA imagining studies also reported that UA narrowing in the obese and non-obese, in normal subjects and apnoeic or snoring patients is predominantly in the lateral dimension due to the thickness of the lateral pharyngeal walls, when compared with weight matched controls (Schwab et al 1995, Mortimore et al 1998, Whittle et al 1999, Tangugsorn et al 2000, Welch et al 2002).

Obesity, especially regional fat deposition in the neck can narrow airway size through deposition of fat around UA and within the soft tissue regions of the neck (Mortimore et al 1998, Whittle et al 1999, Welch et al 2002) and increased pressure on the neck of submental adipose tissue (Ferguson et al 1995). Additionally obesity may promote UA narrowing perhaps by changing resistive loading on the UA (Koenig and Thach 1988). With weight loss, UA volume significantly increases while the volume of the lateral pharyngeal walls and parapharyngeal fat pads are reduced (Rubinstein et al 1988, Shelton et al 1993, Welch et al 2002).

Another possible explanation for the UA narrowing in obese individuals is the fact that obese subjects often have smaller lung volumes, particularly functional residual capacity (FRC), than nonobese subjects (Hoffstein et al 1984). This can have an indirect effect on UA size and contribute to UA narrowing (Deegan and McNicholas 1995).

2.14.3 Combining skeletal factors and obesity

Tangugsorn et al (2000) reported that the non-obese OSAHS patients had more abnormality of skeletal structures, whereas the obese OSAHS patients had more abnormalities in the UA soft tissue morphology, head posture and position of the hyoid bone. In the non-obese patients with OSAHS the shortening of the mandible and maxilla which predispose to UA narrowing may be genetically determined (Mathur and Douglas 1994). Other genetic factors on bony structure, tongue size, and tonsillar tissue can influence UA size. In particular, certain endocrinologic conditions such as hypothyroidism, acromegaly and various genetic disorders (Marfan's syndrome, Pierre-Robin and Treacher-Collins syndromes) predispose to sleep-disordered breathing due to their decreasing UA size, caused by skeletal (e.g. retrognathia) and soft tissue

abnormalities (e.g. macroglossia) (Douglas 2002). However, most patients with sleep-disordered breathing have more subtle anatomical abnormalities that can be detected only using cephalometric or other imaging techniques (Rivlin et al 1984, Ferguson et al 1995).

2.14.4 Other factors: oedema, nasal obstruction and respiratory control instability

Pharyngeal oedema and inflammation in the soft tissue structures caused by the trauma of snoring and recurrent airway occlusions which are delineated in section 2.15 (Pae et al 2005) may perhaps reduce pharyngeal UA size. Active/passive smoking also may influence UA size due to inducing inflammation and oedema in the UA. In a population-based study of 15,555 subjects, Franklin and co-workers (2004) showed that active and passive smoking were associated with snoring, independent of obesity, sex, and age. Oedema due to pre-eclampsia is a potential cause of UA narrowing and partial UA limitation in pre-eclamptic women (Edwards et al 2000b, Connolly et al 2001).

Nasal obstruction is an independent risk factor for habitual snoring regardless of whether AHI $\geq$ 5 or not (Young et al 2001). An extensive computer-assisted review analysing the medical literature on nasal obstruction reported that nasal obstruction is associated with sleep-disordered breathing and can worsen existing sleep-disordered breathing (Rappai et al 2003). Numerous factors can lead to nasal congestion. These factors include anatomic abnormalities such as septal deviation, nasal polyps, hypothyroid myxoedema, adenoid hypertrophy, etc. and mucosal swelling from allergic or nonallergic rhinitis (Rappai et al 2003) or perhaps increased oestrogen level during pregnancy (Edwards et al 2002). Nasal obstruction leads to an increase in airflow velocity and resistance upstream from the collapsible portion of the pharynx and thus

increases negative collapsing pressure. Spontaneous resolution of rhinitis or intranasal steroids can relieve increased nasal airflow resistances due to allergic rhinitis (Rappai et al 2003).

Periodic breathing and respiratory control instability can lead to UA collapsibility and reduction in UA muscles' response to chemical and mechanical stimuli during sleep (Onal et al 1986). Hudgel and colleagues (1998) reported that sleep apnoeic patients have higher loop gain (LG - measure of the stability or instability of a system controlled by feedback loops) than control subjects, measuring LG by pseudorandom binary CO_2 stimulation during wakefulness.

In summary, the interaction between the above factors is important in determining airway size and may have a considerable impact on the development of sleep-disordered breathing. Changes in craniofacial skeletal dimensions and in soft tissue structures may alter UA size.

2.15 Increased neural activation and muscle damage

The trauma which may occur in the UAs of patients with sleep-disordered breathing because of the vibration of tissues during snoring may not only narrow the UA but may also impair the normal function of the receptors responsible for initiating protective reflexes. They also may cause denervation of pharyngeal dilator muscles, or actual damage to the muscles themselves (Wasicko et al 1990, Larsson et al 1992, Leiter 1996, Series et al 1996, Friberg et al 1998, Carrera et al 1999, Kimoff et al 2001, Boyd et al 2004, Pae et al 2005).

UA muscles properties are altered in GG and palatal muscles of habitual snorers and patients with OSAHS, with an abnormally high ratio of type IIa fibres which are less resistant to fatigue compared to type I fibres (Series et al 1996). Treatment of OSAHS by long-term CPAP reduces the proportion of these type IIa fibers (Carrera et al 1999). An animal study also showed that intermittent hypoxia may cause an increase in fatigable fiber types in the geniohyoid muscle (Pae et al 2005). Boyd et al. (2004) performed morphometric analysis on surgically excised UA tissue from nonsnoring control subjects and patients with OSAHS following palatal surgery. The palatal muscles of subjects with OSAHS had inflammatory cells within the UA mucosa (CD4 and CD8; both increased ~threefold) and musculature (predominantly CD4) and direct evidence of denervation compared with control subjects.

Impairment of UA mucosal sensory function has also been detected measuring two-point discrimination and vibratory sensation thresholds, temperature thresholds and investigating the afferent nerve regulation of the microcirculation (Larsson et al 1992, Friberg et al 1998, Kimoff et al 2001). These data are supported by the observation that impairment in the detection of mechanical stimuli is partially reversible after treatment with nasal CPAP in patients with OSA (Kimoff et al 2001).

All the factors mentioned may play a role in the progression of sleep-disordered breathing. However, many may be consequences rather than causes – an issue requiring further study.

2.16 Summary

The pharynx in UA has a collapsible structure due to the lack of bony structure. Both passive mechanical and active neural factors contribute to its patency and collapsibility. Several models are used to explain behaviour of the UA, including the "balance of forces" (airway suction pressure during inspiration versus UA dilator tone) and the Starling resistor model.

The ability of UA muscles to act in response to different conditions is reduced during sleep. This ability includes changes in UA muscle dilator activity and related changes in the mechanics and reflex activity of the muscles. Thus sleep-related changes in UA are the key factors for understanding the mechanism of UA obstruction. Inflammation and trauma which are caused by snoring and other respiratory events may play a role in the progression of sleep-disordered breathing. Presently sleep-disordered breathing is considered to result from a combination of the anatomical UA predisposition and the changes in reflex activity of the muscles during sleep.

CHAPTER 3
THE EFFECT OF PREGNANCY ON THE UPPER AIRWAY AND BREATHING DURING SLEEP

3.1 Introduction

Sleep-disordered breathing is rare in pre-menopausal women, but the risk increases significantly in pregnancy, particularly during the third trimester (Franklin et al 2000). Alterations in the respiratory system during pregnancy due to physiological and hormonal changes affect respiratory function during sleep. These alterations can increase the incidence and severity of sleep-disordered breathing, which may in turn be associated with maternal and foetal impairment during pregnancy. These physiological changes may be particularly marked in females with pre-eclampsia. This chapter reviews these associations.

3.2 Pregnancy-associated sleep disorder

Increasing awareness of the role of sleep disturbances in pregnancy-related complications such as pre-eclampsia have generated growing interest in further investigation of sleep disorders during pregnancy amongst both the obstetrical and sleep research professionals. Therefore a "pregnancy-associated sleep disorder" is identified as a distinct clinical disorder in the International Classification of Sleep Disorders (ICSD). It begins with excessive sleepiness and progresses to severe insomnia (American Academy of Sleep Medicine 2001). The most common reason given for sleep alterations is discomfort due to the gravid uterus and pregnancy-associated physiological changes, including high concentration of sex steroids and sleep complaints such as snoring, nocturnal awakenings (Karacan et al 1968, Driver and Shapiro 1992, Hertz et al 1992, Guilleminault et al 2000, Lee et al 2000). While pregnant women may rarely experience

sleep disorders such as nightmares or sleep terrors (Karacan et al 1969, American Academy of Sleep Medicine 2001), they can suffer from lack of concentration, irritability, apathy, and moodiness, which may be linked with sleep-disordered breathing. This chapter will focus primarily on sleep-disordered breathing events in pregnancy rather than other pregnancy-associated sleep disorders.

3.3 The risk of sleep-disordered breathing in pregnancy

The multiple pregnancy specific factors which may influence breathing during sleep are reviewed below.

3.3.1 Pregnancy-associated changes that increase the risk of sleep-disordered breathing

3.3.1.1 Gestational weight and neck circumference

As mentioned in chapters 1 and 2, gaining weight in the form of obesity is a major risk factor for sleep-disordered breathing and findings from a population-based epidemiologic study strongly supported this connection between weight and symptoms of sleep-disordered breathing (Young et al 1993). In pregnancy, weight gain and physical inactivity combined with other adaptations may exacerbate pre-existing sleep-disordered breathing or contribute to the development of sleep-disordered breathing. Franklin and Maasilta et al noted that habitual snorers were significantly heavier than non-snorers both before and during pregnancy (Franklin et al 2000, Maasilta et al 2001). Lueng et al (2005) reported that women with a baseline BMI > 25 kg/m^2 show significantly more moderate to severe snoring intensity than those with BMI <25 kg/m^2. Additionally, case reports of gestational OSAHS showed that pregnant women who developed OSAHS were consistently obese. A recent systematic review of controlled studies of pre-

eclampsia reported that higher baseline BMI is also a risk factor for pre-eclampsia (Duckitt and Harrington 2005).

Weight gain is known to be a risk factor for developing sleep-disordered breathing (Young et al 1993, Peppard et al 2000a, Horner et al 1989, Mortimore et al 1998) especially when associated with increased neck size in females (Deegan and McNicholas 1996). In the general population neck size is a predictor of the likelihood of sleep-disordered breathing, independent of weight (Davies et al 1992). Studies with non-pregnant women also found that pharyngeal cross-sectional area and FRC increased with weight loss (Hoffstein et al 1984, Rubinstein et al 1988, Welch et al 2002).

Larger neck size during pregnancy may increase the tendency for UA collapse during sleep (Edwards et al 2002). The fat deposition due to weight gain during or prior to pregnancy, especially fat which is within the soft tissue regions of the neck, could cause pharyngeal narrowing and contribute to sleep-disordered breathing in pregnant women (Horner et al 1989, Mortimore et al 1998), or exacerbate the existing sleep-disordered breathing in pregnancy. Imaging studies are needed to clarify this issue in pregnant women with sleep-disordered breathing.

3.3.1.2 Changes in the upper airway

Semi-quantitative gross physical inspection has suggested that pharyngeal dimensions decrease during pregnancy, based on the Mallampati score (Pilkington et al 1995) in the first and third trimesters. Engorgement, hypersecretion and mucosal oedema occur in the UA due to the progressive increase in oestrogen levels. These changes may lead to a reduction in pharyngeal and nasal dimensions (Elkus and Popovich 1992, Pilkington et

al 1995, Sahota et al 2003, Guilleminault et al 2004) independent of any extrinsic compression of the airway.

Increased blood and interstitial fluid volumes or rhinitis of pregnancy, which occurs in 22%-42% of pregnant women, are also very common problems, causing nasal obstruction during pregnancy (Ellegard et al 2000, Bende and Gredmark 1999). Increased nasopharyngeal resistance may make the airway pressure more negative during inspiration and contribute to the collapse of the pharyngeal airway during sleep.

Elevated ventilatory drive due to increases in progesterone level may induce obstructive sleep-disordered breathing by increasing diaphragmatic effort which leads to greater negative inspiratory pressures in the UA (Remmers et al 1978). This may increase the tendency for the airway to collapse during sleep.

Sleep disturbance and fatigue are common complaints among pregnant women (Hertz et al 1992, Suzuki et al 1994). Studies in other clinical populations showed that sleep fragmentation and sleep deprivation decreased UA muscle activity and increased UA collapsibility (Leiter et al 1985, Series et al 1994). The contribution of sleep disturbance and fatigue to the pathogenesis of sleep-disordered breathing in pregnancy requires further study.

3.3.1.3 Changes in lung mechanics and blood gas tensions

The total lung capacity, vital capacity and closing capacity did not change significantly during pregnancy (Gee et al 1967, Craig and Toole 1975, Holdcroft et al 1977). However elevation of the diaphragm due to abdominal mass loading, relaxation of the

costochondral ligaments and the compensatory increase in the anterior-posterior diameter of the chest lead to tracheal shortening, and FRC falls by 15-25%, expiratory reserve volume by 33–40% and residual volume by 22 % (Gee et al 1967, Craig and Toole 1975, Holdcroft et al 1977, Hoffstein et al 1984, Bourne et al 1995).

Decreased FRC and tracheal shortening may cause small airway closure especially in the supine position (Craig and Toole 1975, Hoffstein et al 1984, Burger et al 1992, Holdcroft et al 1977, Stanchina et al 2003). Decreased FRC may also cause changes in the arterial oxygen level due to decreasing oxygen stores (Craig and Toole 1975). The closure of small airways during normal tidal breathing results in ventilation perfusion mismatch and reduced gas exchange in late pregnancy, leading to low arterial oxygen tensions (PaO2) (Craig and Toole 1975, Holdcroft et al 1977).

3.3.1.4 Ventilation and respiratory gases

Hyperventilation due to increased progesterone levels causes respiratory alkalosis with partial pressure of carbon dioxide (PCO_2) slightly lower and partial pressure of oxygen (PO_2) slightly higher than normal. Decreased levels of arterial carbon dioxide tension ($PaCO_2$) during pregnancy could potentially induce periodic breathing at sleep onset which has been shown to contribute to sleep-disordered breathing. These changes may result in respiratory instability and episodes of central sleep apnoea during non-REM sleep (Skatrud and Dempsey 1983).

3.3.2 Pregnancy-associated changes that reduce the risk of sleep-disordered breathing

There are some factors which potentially could decrease O_2 desaturation and sleep-disordered breathing during pregnancy. High levels of progesterone will tend to cause hyperventilation, reducing PCO_2 at the central chemoreceptors (White et al 1983, Polo and Ekholm 1995) and tending to protect UA patency, by increasing UA dilators muscle activity (Popovic and White 1995, Saaresranta et al 2003).

In normal pregnancy, blood volume increases by 40% to 50% from 6-8 weeks gestation, to 32-34 weeks with little change thereafter (Ciliberto and Marx 1998). Increases in plasma and red cell volumes lead to a rise in intravascular volume. Cardiac output in the first trimester is 12% to 20% higher than in the non-pregnant state, rising to an average of 50% above pre-pregnant levels in the third trimester, while heart rate increases by around 29% and stroke volume by around 18% (Mabie et al 1994). These changes in the cardiovascular system and the right shifted oxyhaemoglobin dissociation curve both improve delivery of O2 to the placenta and maternal tissue (Mesa et al 1999).

In late pregnancy, women spend less time supine and more time in the lateral position during sleep which helps to increase cardiac output, stroke volume and oxygenation (Milsom and Forssman 1984, Hertz et al 1992, Lefcourt and Rodis 1996, Maasilta et al 2001).

Decreased REM sleep and recurrent awakenings during sleep (Karacan et al 1969, Hertz et al 1992, Lee et al 2000, Hedman et al 2002) also may protect pregnant women from sleep-disordered breathing events.

3.4 Changes in sleep architecture and sleep quality in pregnancy and postpartum

During the first trimester, total sleep time (TST), daytime sleepiness, nocturnal awakenings, and insomnia increase and overall sleep quality and slow wave sleep (SWS) decreases (Lee et al 2000, American Academy of Sleep Medicine 2001, Hedman et al 2002). Sleep is more normal in the second trimester when the percentage of SWS increases compared to the first trimester (Driver and Shapiro 1992, Karacan et al 1969, Suzuki et al 1994, American Academy of Sleep Medicine 2001). However, at the end of the second trimester (23-24 weeks of gestation), TST falls (Lee et al 2000) and the prevalence of restless sleep and sleep complaints increase (Schweiger 1972).

In the third trimester, increased awakenings after sleep onset, unrefreshing sleep, increased daytime sleepiness and impaired daytime alertness were reported and sleep quality was often poor (Hertz et al 1992, Suzuki et al 1994, Schorr et al 1998, American Academy of Sleep Medicine 2001).

During late pregnancy, stage 1-2 sleep significantly increased, sleep stages three and four were shortened (Karacan et al 1969, Hertz et al 1992, Brunner et al 1994, Schorr et al 1998, Lee et al 2000) and sleep efficiency decreased compared with non-pregnant women (Driver and Shapiro 1992, Hertz et al 1992, Brunner et al 1994, Lee et al 2000). Daytime sleepiness increased in up to 65% of pregnant women by the end of pregnancy due to sleep disturbances (Franklin et al 2000). Reasons for these disturbances in the third-trimester include urinary frequency, backache, foetal movement, uterine activity, general abdominal discomfort, leg cramps, restless legs syndrome, heartburn and repetitive UA obstructions (Driver and Shapiro 1992, Hertz et al 1992, Seron-Ferre et al

1993, Brunner et al 1994, Suzuki et al 1994, Edwards et al 2000a, Franklin et al 2000, American Academy of Sleep Medicine 2001, Hedman et al 2002). Uterine activity, which is linked with circulation of melatonin, and oxytocin have also significant effects on sleep patterns (Seron-Ferre et al 1993), as have oestrogen and progesterone.

Decreased REM sleep during pregnancy may prevent apnoeic events, but sleep onset and arousal from sleep destabilize respiration (Pillar et al 2000b, Tangel 1991, Worsnop et al. 1998, 2000, Fogel et al 2003c, Fogel et al 2003b). Thus, increased sleep stages 1 and 2 in late pregnancy and frequent awakenings from sleep may increase the risk of sleep-disordered breathing and may affect the frequency of sleep-disordered breathing events (Karacan et al 1969, Hertz et al 1992, Lee et al 2000).

Following delivery, the degree of maternal sleep disturbances increases considerably during the first month (Lee et al 2000). REM sleep decreases and then normalizes after two weeks, and stage 4 sleep comes back to pre-pregnancy level (American Academy of Sleep Medicine 2001, Edwards et al 2005). Both sleep latency and REM sleep latency are markedly decreased (Edwards et al 2005). However TST and sleep efficiency remain low for up to 3 months (Karacan et al 1968, Lee et al 2000, Hedman et al 2002) probably due to the need to feed the baby, the infant's circadian rhythm and hormonal changes (Hertz et al 1992, Lee et al 2000). Research by Blyton et al showed marked increases in SWS in breast-feeding women as compared with those who bottle-fed their infants or controls. The most likely explanation for this alteration in sleep architecture postpartum is the increase in circulating prolactin, which occurs in lactating women (Blyton et al 2002).

3.5 Sleep disordered breathing in pregnancy

3.5.1 Snoring

Snoring is common among pregnant women (Loube et al 1996, Franklin et al 2000, Guilleminault et al 2000), perhaps due to engorgement, hypersecretion and mucosal oedema in the UA which induce UA narrowing (Pilkington et al 1995). Loube et al found that 14% of 350 healthy pregnant women snored frequently during the second or third trimesters, compared to 4% of matched non-pregnant women. The percentage of snoring may be greater than that because the questionnaires were given only to women attending the "non-risk" antenatal clinics in this study (Loube et al 1996). Franklin et al reported that 23% of 502 pregnant women reported on the day of delivery that they were habitual snorers. Four percent of them reported being habitual snorers before pregnancy, but this study did not have a control group to compare with non-pregnant women (Franklin et al 2000). Another questionnaire study showed that recurrent and loud snoring "increased" non-significantly during pregnancy from 5% before pregnancy to 10.4% in the third trimester, but decreased significantly to 4.4% after the delivery (Hedman et al 2002). The prevalence of snoring in pregnancy could be higher than these figures, because women generally tend to under-report their snoring (Redline et al 1994). In a prospective study aiming to evaluate the severity of snoring as scored by the bed-partner at 6 weeks and 6 months into normal pregnancy, 18% of 267 pregnant women at the 6-week and 52% of the 128 who consented to enroll in part 2 at 6-month were reported to snore at least intermittently. ($p=0.001$) (Guilleminault et al 2000). It has also been demonstrated using PSG that airflow limitation and increased respiratory effort were common in these women. The chronic loud snorers spent between 61% and 92% of TST with snoring (Guilleminault et al 2000).

3.5.2 Oxygen desaturation during sleep

The low FRC during pregnancy will predispose to O_2 desaturation which would be worse in the supine position during sleep (Craig and Toole 1975, Bourne et al 1995, Trakada et al 2003). Guilleminault et al showed that 13% of 267 pregnant women had SaO_2 drops ≥5%, at least once during the night. The mean of O_2 desaturation index (ODI: the number of SaO_2 drops of ≥3% per hour of sleep) was 2 events/hr (range 3–7 events/hr) (Guilleminault et al 2000).

Normal pregnant women have also been reported to exhibit mild O_2 desaturations during sleep. The mean overnight SaO_2 in the non-pregnant group (98.5%) was significantly higher than in normotensive pregnant women or women with pregnancy-induced hypertension (both 95%) (Bourne et al 1995).

Hertz and colleagues (1992) also reported that 12 women during the third trimester of pregnancy had a small but significant reduction in nocturnal SaO_2 compared to the postpartum period of the same subjects. In another study, PaO_2 levels in the supine position during sleep were significantly lower during pregnancy compared to the postpartum period (Trakada et al 2003). In contrast, Brownell et al (1986) reported that there were no significant changes in oxygenation during sleep in healthy subjects between 36 weeks gestation and postpartum period.

3.5.3 OSAHS during pregnancy and postpartum

Although the prevalence of OSAHS in women of reproductive age is approximately 5% (Young et al 1993), the precise prevalence of OSAHS during pregnancy is unknown.

Large prospective studies showing an association between pregnancy and sleep apnoea are lacking (Guilleminault et al 2000).

There is no clear evidence on the frequency of clinical sleep-disordered breathing during pregnancy. Most of the data on OSAHS during pregnancy comes from case reports, which are presented in table 3.1 (Joel-Cohen and Schoenfeld 1978, Conti et al 1988, Hastie et al 1989, Kowall et al 1989, Schoenfeld et al 1989, Charbonneau et al 1991, Pieters et al 1995, Lefcourt and Rodis 1996, Lewis et al 1998, Taibah et al 1998, Brain et al 2001, Roush and Bell 2004). Some suggest that pregnancy may precipitate or exacerbate OSAHS especially in obese women (Hastie et al 1989, Kowall et al 1989, Charbonneau et al 1991, Lefcourt and Rodis 1996, Lewis et al 1998, Brain et al 2001).

Table 3.1 Case reports of sleep disordered breathing in pregnancy

Study	n	Pregnancy Complication	Method of Diagnosis	AHI	Treatment	Birth Outcome
Joel-Cohen and Schoenfeld	3	None	Clinical examination	NA	None	1 infant had intrauterine growth restriction information on remaining births not available
Schoenfeld et al.	8	None	Clinical examination	NA	None	All 8 infants had intrauterine growth restriction
Conti et al.	1	Preeclampsia	Clinical examination	NA	None	Normal birthweight infant
Kowall et al.	1	Preeclampsia	Polysomnography	78.6	CPAP	NA
Hastie et al.	1	Gestational diabetes mellitus	Polysomnography	42.5	Tracheostomy	Normal birthweight infant
Charbonneau et al.	1	Gestational diabetes mellitus	Polysomnography	159	CPAP	Intrauterine growth restriction
Lefcourt et al.	1	Preeclampsia	Clinical examination	NA	None	Intrauterine growth restriction
Lewis et al.	1	Pulmonary hypertension	Clinical examination	NA	Oxygen CPAP	Normal-birthweight infant
Taibah	1	hypothyroidism	Polysomnography	128	L-thyroxin (100 mcg)	NA
Pieters et al.	1	None	Polysomnography	0(Central alveolar hypovent)	NIPPV	Normal-birthweight infant
Brain et al.	1	PIH	Clinical examination Polysomnography	30	CPAP	Growth restriction and foetal death.
Roush et al	1	Preeclampsia	Polysomnograph	160	CPAP	Intrauterine growth restriction

Abbrevations: PIH = pregnancy-induced hypertension, NIPPV = nasal intermittent positive pressure ventilation

Brownell and Trakada et al reported that the prevalence of apnoea and hypopnoea was significantly lower during pregnancy compared with the postpartum period, but the subjects of these studies were healthy pregnant women with no evidence of sleep-disordered breathing before the pregnancy (Brownell et al 1986, Trakada et al 2003). In a larger study, PSG was performed with esophageal manometry on 26 women after the sixth month of pregnancy, 13 loud snorers and 13 non-snorers. None of these women had frank obstructive sleep apnoea, but the chronic snorers were more likely to have "UARS". The impact of pregnancy on UA had ceased a few months after delivery (Guilleminault et al 2000). Likewise, a study of 10 women with multiple pregnancies (Nikkola et al 1996) noted there were no significant sleep apnoeas or events of hypoxemia in the third-trimester of pregnancy, although their sleep quality was impaired.

A case-control study by Maasilta et al (2001), examining the relationship between obesity and gestational sleep-disordered breathing, also verified that normal pregnancy does not contribute to sleep apnoea in non-obese women. However, in the same study the mean AHI of obese women significantly increased from 1.7 in early pregnancy to 2.6 events/hr in late pregnancy, although this increase is not clinically important. Pre-eclampsia and mild OSAHS occurred in only one obese mother.

3.6 Pregnancy complications associated with sleep-disordered breathing

3.6.1 Maternal complications

There is limited evidence regarding possible complications of sleep-disordered breathing during pregnancy. Franklin et al speculated that nocturnal UA obstruction may

contribute to pre-eclampsia and pregnancy-induced hypertension (PIH) and intrauterine growth retardation because in their study all habitual snorers started to snore before developing pre-eclampsia. However it is not possible to draw any conclusions regarding cause and effect owing to the retrospective, cross-sectional design of the study, and the researchers did not control possible confounding factors, such as BMI and parity (Franklin et al 2000). Similar adverse outcomes: PIH, pulmonary hypertension, pre-eclampsia and diabetes (Table 3.1), have been reported in cases of OSAHS in pregnancy (Conti et al 1988, Hastie et al 1989, Kowall et al 1989, Lefcourt and Rodis 1996, Lewis et al 1998, Brain et al 2001, Roush and Bell 2004).

Several studies have examined the association between pre-eclampsia and sleep-disordered breathing in pre-eclamptic women and noted that pre-eclamptic subjects did not have evidence of clinically significant OSAHS (Edwards et al 2000b, Connolly et al 2001). The respiratory abnormality which was detected in patients with pre-eclampsia was an increase in sleep-induced flow limitation with characteristic low-frequency flow oscillations affecting on average 72% of breaths during sleep which occur in SWS (Edwards et al 2000b). These episodes are similar to the pattern of respiratory events found in UARS, which is one of transient episodes of inspiratory flow limitation, often terminated by arousal (Guilleminault and Chowdhuri 2000, American Academy of Sleep Medicine 2001, Connolly et al 2001). However in pre-eclamptic women these episodes continue for several minutes and are associated with blood pressure surges (Edwards et al 2000b, Edwards et al 2001).

A characteristic of hypertension associated with pre-eclampsia is normally the absence of the normal nocturnal dip in blood pressure or decrease in day-night blood pressure

difference (Halligan et al 1996). This "non-dipper" pattern is also found in OSAHS. A well-controlled randomised trial from our department showed that "non-dippers" with OSAHS had a significant improvement in daytime mean arterial blood pressure on CPAP compared to placebo (Engleman et al 1996). Another much larger randomised controlled trial again from our department has confirmed this finding, showing that both night-time blood pressure and 24 hour blood pressure in OSAHS were decreased by CPAP treatment in patients with an unselected group of patients with OSAHS (Faccenda et al 2001). This has been confirmed by others (Pepperell et al 2002; Becker et al 2003).

Furthermore, there is growing evidence that the intermittent episodes of hypoxia and reoxygenation associated with sleep-disordered breathing can be a strong stimulus for oxidative stress (Lavie 2003, Roberts and Hubel 2004, Ryan et al 2005), although this has been disputed (Svatikova et al 2005). These repeated changes of oxygen saturation could be considered analogous to recurrent episodes of placental hypoxia/reperfusion in pre-eclampsia, which causes damage after the restoration of blood flow to ischaemic or hypoxic tissues which is explained more below (3.8.3) (Chambers et al 2001, Roberts and Lain 2002, Duley 2003). Elevated production of free radicals during hypoxia-reoxygenation predisposes to endothelial dysfunction (Roberts and Cooper 2001, Lavie 2003, Guilleminault and Abad 2004, Heitmann et al 2004). Endothelial dysfunction may underlie many of the manifestations of pre-eclampsia and the vascular associations of OSAHS (Edwards et al 2001, Granger et al 2001, Lavie 2003). However, whether intermittent hypoxia induced by sleep-disordered breathing can account for the elevated levels of reactive oxygen species (ROS) and endothelial dysfunction associated with pre-eclampsia is unclear.

A study by Edwards et al has demonstrated that blood pressure and heart rate responses to cyclic respiratory events during sleep were markedly increased in women with pre-eclampsia and coexisting OSAHS compared with pregnant women with OSAHS but no hypertension (Edwards et al 2001). They proposed that these increased pressor responses to obstructive events during sleep in pre-eclamptic women occur as a result of maternal endothelial damage induced by the pre-eclampsia disease process and thus may be responsible for the overall increase in blood pressure that occurs in pre-eclampsia (Edwards et al 2001).

These findings suggest that a common link occurs during sleep between sleep-disordered breathing and pre-eclampsia and this may to some extent be due to intermittent episodes of hypoxia and reoxygenation.

3.6.2 Foetal complications

The effects of prolonged snoring on alveolar ventilation suggest that intermittent maternal hypoxia throughout many weeks of pregnancy can cause adverse outcomes on the developing foetus including foetal growth restriction (Joel-Cohen and Schoenfeld 1978, Schoenfeld et al 1989, Charbonneau et al 1991, Roush and Bell 2004). Many neurohormones including the growth hormone produced during sleep may be affected by sleep fragmentation due to obstructive events. In animal models, it has been shown that gestational intermittent hypoxia leads to significant reductions in foetal growth (Gozal et al 2003). Some case reports of pregnancy complicated by OSAHS and pre-eclampsia also indicate a possible connection with intrauterine growth retardation, foetal death, and evidence of foetal compromise, OSAHS and pre-eclampsia (Joel-Cohen and

Schoenfeld 1978, Lefcourt and Rodis 1996, Lewis et al 1998, Brain et al 2001, Roush and Bell 2004).

In preeclamptic women, reduced placental perfusion combined with the impact of endothelial activation, both of which could be potentially exacerbated by sleep-disordered breathing, may affect the foetus' condition. Roush et al reported that a witnessed apnoeic episode with maternal O_2 desaturation occurred in a preeclamptic patient concurrently with foetal heart rate decceleration (Roush and Bell 2004). Joel-Cohen and Schoenfeld also reported that foetal heart rate abnormalities associated with maternal obstructive respiratory events during sleep (Joel-Cohen and Schoenfeld 1978). Blyton et al showed that in pre-eclamptic women there was a rise in total peripheral resistance, a reduction in cardiac output during sleep and a significant correlation between maternal cardiac output and foetal birth weight. Reductions in cardiac output and increments in total peripheral resistance were reversed with nasal CPAP [this study is discussed in more detail below (3.10)]. This evidence suggests that maternal cardiac output during sleep may be important to foetal growth. Authors proposed that reduction in placental blood flow during maternal sleep may be specifically limiting to fetal growth and harmful to well-being (Blyton et al 2004).

Franklin and colleagues (2000) reported that habitual snorers were more than twice as likely as non-snorers to give birth to an infant with intrauterine growth retardation or with an Apgar score less than 7 at both 1 and 5 minutes. After adjustment for maternal age, weight, and smoking habits, differences remained significant and odds ratio for associations with frequent snoring was 3.5 (95% CI 1.3–9.4) for intrauterine growth

retardation. However, these findings were obtained from retrospective data, and thus recollection of symptoms may have biased results.

On the contrary, Loube and coworkers (1996) did not find any significant differences in birth weight, Apgar score, or frequency of perinatal complications between infants born to women with or without frequent snoring during the second or third trimester of pregnancy. Likewise, Hedman et al reported that there was not a significant relationship between snoring and infant birth weight in a prospective survey of sleep symptoms, but 52% of the subjects could not be followed-up in this study (Hedman et al 2002).

3.7 Hypertensive disorders in pregnancy

In normal pregnancy, maternal blood pressure falls reaching lowest levels at around 16 to 20 weeks' gestation. Blood pressure increases after 28 weeks and returns to non-pregnant values toward the end of the third trimester (Longo et al 2003).

The classification of hypertensive disorders in pregnancy has been simply organised to reflect the different situations encountered in clinical practice (Duley 2003, Longo et al 2003). The classification and description of these disorders are given in table 3.2 (Longo et al 2003). During pregnancy, PIH also called gestational hypertension occurs in 6–7% of pregnancies (table 3.2). This thesis primarily focuses on pre-eclampsia because of its connection with sleep-disordered breathing.

Table 3.2 Classification of Hypertensive Disorders in Pregnancy *(From Longo, South Med J. 2003; 96(9):891-9).*

Disorders	Definitions
Chronic hypertension	Hypertension present before pregnancy or first diagnosed before 20 weeks' gestation
Preeclampsia-eclampsia	New hypertension (>140 mm Hg systolic or >90 mm Hg diastolic pressure on at least two occasions and at least 4–6 h apart) and proteinuria (excretion >0.3 g in 24 h or 1+ on dipstick) after 20 weeks' gestation in a previously normotensive woman
	Eclampsia if seizures also occur
Preeclampsia superimposed on chronic hypertension	New-onset or acutely worse proteinuria, sudden increase in blood pressure, thrombocytopenia, or elevated liver enzymes after 20 weeks' gestation in women with preexisting hypertension
Gestational hypertension	Increased blood pressure (>140 mm Hg systolic or >90 mm Hg diastolic pressure) first diagnosed after 20 weeks' gestation and not accompanied by proteinuria
Transient hypertension	Hypertension resolves by 12 weeks postpartum
Chronic hypertension	Hypertension does not resolve by 12 weeks postpartum

3.8 Preeclampsia

Pre-eclampsia, a major cause of maternal and perinatal mortality, is more than simple hypertension during pregnancy. As Roberts and Lain (2002) stated: "It is secondary to the interactions of reduced placental perfusion with diverse maternal factors". This causes endothelial dysfunction which results in abnormal regulation of blood vessel tone and thus influences almost every organ system of the body (Roberts and Lain 2002,

Yinon et al 2006) as delinated below. It occurs in 2–10 % and eclampsia in < 1% of pregnancies (Duckitt and Harrington 2005, Roberts and Cooper 2001, Duley 2003, Longo et al 2003, Sibai et al 2005).

3.8.1 Risk factors for pre-eclampsia

A recent systematic review of controlled studies (Duckitt and Harrington 2005) and other studies (Roberts and Cooper 2001, Longo et al 2003, Sibai et al 2005) reported that previous pre-eclampsia, extremes of maternal age, multiple pregnancies, family history, primiparity/ nulliparity, a gap of >10 years since last pregnancy, higher baseline BMI, hypertension, increased blood pressure at booking, augmented blood homocysteine concentration, and pre-existing renal disease and diabetes all increased the risk of a woman developing pre-eclampsia. Obesity and ageing are also major risk factors for sleep-disordered breathing, while hypertension, renal disease, increased insulin resistance and elevated plasma homocysteine concentration are also associated with sleep-disordered breathing (Peppard et al 2000b, Roberts and Cooper 2001, Longo et al 2003, Duckitt and Harrington 2005, Sibai et al 2005). Therefore, a link between pre-eclampsia and sleep-disordered breathing may occur through these factors in pre-eclamptic women with co-existing snoring and sleep apnoea.

3.8.2 Sleep quality and sleep architecture in pre-eclampsia

Sleep quality and sleep architecture in women with pre-eclampsia have not been extensively studied. Previous studies reported that sleep quality was impaired in pre-eclamptic women (Ekholm et al 1992, Blyton et al 2004). Edward et al (2000a) found that pre-eclamptic subjects had markedly altered sleep architecture, with a significant increase in SWS and a decrease in REM sleep. Pre-eclamptic women have a high risk for

developing sleep-disordered breathing (Edwards et al 2000b, Connolly et al 2001, Franklin et al 2000). Whether these changes in sleep architecture in pregnancy and pre-eclampsia are directly related to the occurrence of sleep-disordered breathing events requires further study.

3.8.3 Pathogenesis of pre-eclampsia

The pathogenesis and mechanisms of pre-eclampsia without pre-existing conditions are not well understood, but there are different theories about them. Preeclampsia is usually considered to be a 2-stage disorder. The first stage is reduced placental perfusion and the second stage is the maternal response to this condition, characterized by widespread inflammation and maternal endothelial cell dysfunction (Roberts and Lain 2002). This current concept is important for this thesis because vascular endothelium dysfunction and oxidative stress are also associated with sleep-disordered breathing. A recent study reported that both sleep-disordered-breathing and endothelial dysfunction occur more often in women with pre-eclampsia than in women with uncomplicated pregnancies (Yinon et al 2006). On the other hand, genetic factors might also predispose to pre-eclampsia, but the contributions of maternal and foetal genotypes are still not clear.

●The reduction in uteroplacental perfusion: Poor placental perfusion is considered to be the root cause of pre-eclampsia. Placental perfusion is maybe reduced secondary to abnormal implantation and development of the placental vasculature as a result of incomplete invasion of the trophoblastic cells into the uterus (Lain and Roberts 2002, Granger et al 2001, Edwards et al 2001).

This insufficient uteroplacental circulation leads to placental ischaemia, placental hypoxia, oxidative stress and release of ROS which damage the maternal vascular endothelium (Chambers et al 2001, Roberts and Lain 2002, Duley 2003, Longo et al 2003). Most importantly, intrauterine growth retardation occurs as a result of placental ischaemia prior to the manifestation of pre-eclampsia (Roberts and Lain 2002). However, placental factors are not solely accountable for the maternal constellation of signs and symptoms, or syndrome. Maternal factors (genetic, environmental, and behavioral) must interact with the reduced placental perfusion in order for the maternal manifestations of pre-eclampsia, such as high blood pressure, to appear. This paradox has produced the concept of pre-eclampsia as a two-stage disorder (Roberts and Lain 2002, Lain and Roberts 2002).

●**Oxidative stress:** The link between the pathophysiology of abnormal placentation and that of the maternal syndrome remains unclear. There is increasing evidence that pre-eclampsia is associated with both increased oxidative stress and reduced antioxidant defences (Chambers et al 2001, Roberts and Lain 2002). This supports the hypothesis that oxidative stress may play a critical role in the pathogenesis of pre-eclampsia, perhaps linking stages 1 and 2, resulting in the clinical manifestations of pre-eclampsia (Lain and Roberts 2002).

Maternal endothelial cell dysfunction is a key factor in the development of the clinical manifestations of pre-eclampsia (Hubel 1999*)*. Oxidative stress is likely involved in endothelial cell dysfunction in pre-eclampsia. Several studies have investigated oxidative stress-related molecules in pre-eclamptic pregnancies. The serum levels of oxidative stress-related molecules, such as lipid peroxides and malondialdehyde (MDA), have

been found to be higher in pre-eclamptic women while antioxidants such as vitamins E and C were significantly decreased compared to healthy pregnant women (Madazli et al 1999).

Oxidative stress can be defined as an imbalance between ROS and antioxidants, favouring an overabundance of ROS (Chambers et al 2001, Roberts and Lain 2002, Duley 2003, Longo et al 2003). The generation of ROS leads to lipid peroxidation and subsequent endothelial cell injury, and oxidative damage to proteins and nucleic acids (Pipkin 1995, Chambers et al 2001, Roberts and Lain 2002, Roberts and Hubel 2004). During hypoxia/reperfusion the initial response is an increase in the generation of ROS. Excess free radicals are normally eliminated by antioxidant systems. However, when ROS generation exceeds the capacity of antioxidant mechanisms to eradicate them, oxidative stress and damage to cells and tissues follow (Lavie 2003, Roberts and Hubel 2004). Hypoxia/reperfusion may occur due to both placental and maternal factors. Moretti and colleagues (Moretti et al 2004) measured oxidative stress in exhaled breath and demonstrated that oxidative stress in women with pre-eclampsia was significantly greater than in those with uncomplicated pregnancies and non-pregnant controls. Maternal hypoxia may increase the production of ROS on reoxygenation (Roberts and Hubel 2004).

Sharma et al (2006) reported that oxidative stress markers such as blood levels of glutathione peroxidase (GPX), superoxide dismutase (SOD), and serum levels of MDA were significantly higher in women with pre-eclampsia than in controls, and the plasma levels of vitamin C and lycopene were significantly lower in women with pre-eclampsia than in controls.

Uzun et al (2005) found that serum concentrations of lipid parameters such as total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TGs) were significantly higher in pre-eclampsia compared with controls. Serum concentrations of MDA and oxidized low-density lipoprotein (oxLDL) were significantly higher, while paraoxonase (PON1) activity was significantly lower in pre-eclampsia compared with controls.

These data demonstrate that pre-eclampsia is associated with increased markers of oxidative stress (such as lipid peroxidation products and anti-oxidized LDL antibodies) and reduced antioxidants. Both these may cause vascular endothelial damage and contribute to the pathophysiology of pre-eclampsia (Hubel (1999). Abnormalities in endothelial function are also associated with sleep-disordered breathing due to intermittent episodes of hypoxia and reoxygenation (Lavie 2003). A review article (Foster et al 2007) referring to animal studies reported that intermittent hypoxia leads to oxidative stress, inflammation and reduction in the level of antioxidants. All this suggests an association between pre-eclampsia and sleep disordered breathing. Therefore, measures such as biomarkers of oxidative stress would be valuable variables in this study, but we did not have the resources to obtain them.

●Endothelial dysfunctions: Endothelial dysfunction has been considered a major contributor in the pathogenesis of pre-eclampsia. The endothelial cells normally maintain vascular integrity, regulate the smooth muscle tone through release of vasoconstrictor and vasodilatory substances, and prevent antiadhesive and anticoagulant properties (Edwards et al 2001, Granger et al 2001). The loss of these atheroprotective properties of the normal endothelium is termed endothelial dysfunction.

There is evidence supporting the hypothesis that the ischaemic placenta contributes to endothelial cell activation/dysfunction of the maternal circulation by increasing the production of cytokines such as tumor necrosis factor-a (TNF-α) (Granger et al 2001). TNF-α release oxidizing free radicals and format lipid peroxides, destabilizing electron flow in mitochondria. Lipid peroxides and oxygen radicals can damage endothelial cells (Granger et al 2001).

Endothelial dysfunction results in abnormal regulation of blood vessel tone, vasospasm with consequent reduction in plasma volume, activation of the coagulation cascade and potentially hypertension (Edwards et al 2001, Granger et al 2001, Roberts and Lain 2002). These changes occur before other clinical findings of pre-eclampsia (Chambers et al 2001, Duley 2003). This suggests that endothelial dysfunction may be a causative factor rather than an outcome of pre-eclampsia.

●**Genetics factors:** Both maternal genes and foetal genes (from either the mother or father) may trigger pre-eclampsia but the maternal factors are stronger than the foetal factors (Roberts and Cooper 2001, Sibai et al 2005, Skjærven et al 2005). A population based cohort study by Skjærven et al (2005) examined 438,597 mother-offspring units and 286,945 father-offspring units from the Norwegian medical birth registry. Women with clinically severe or early onset pre-eclampsia were more likely to have been born after a pre-eclamptic pregnancy compared with women born after an unaffected pregnancy (3.0, 95% CI 2.4-3.7). Men born after a pre-eclamptic pregnancy were also more likely to have fathered a pregnancy with severe or early pre-eclampsia (1.9, 95% CI 1.4-2.5). These findings suggest that existing pre-eclampsia history in a family predicts more severe pre-eclampsia.

Changed paternity in multiparous women and cohabitation (a period of exposure to paternal antigens) also can affect susceptibility for eclampsia and pre-eclampsia. However, men who themselves were born after a pre-eclamptic pregnancy may have a moderately increased risk of fathering a pre-eclamptic pregnancy (Roberts and Cooper 2001).

3.8.4 Presentation and diagnosis of pre-eclampsia

Hypertension in a mother with a previously normal blood pressure and proteinuria are considered to be the hallmarks of pre-eclampsia (Pipkin 1995, Longo et al 2003, Sibai et al 2005). Oedema is no longer part of most current definitions of pre-eclampsia due to it being a common feature of normal pregnancy (Longo et al 2003). Obtaining a careful history, physical examination and laboratory evaluation may clarify the diagnosis. Precise diagnosis of pre-eclampsia depends on careful blood pressure measurements - that is taken on a rested subject who is seated or lying on the left side, positioning the arm at heart level, proper cuff size, and calibration of equipment - and the amount of protein found in the urine over a 24 h period (excretion >0.3 g/d) (Pipkin 1995, Longo et al 2003, Sibai et al 2005).

Blood pressure greater than 130/80 mm Hg usually requires close surveillance (Longo et al 2003). If systolic blood pressure is greater than 160 mm Hg or diastolic blood pressure greater than 110 mm Hg with significant proteinuria (>5.0 g/d), it is classified as severe pre-eclampsia. The following signs and symptoms are commonly observed in severe pre-eclampsia; pulmonary oedema, oliguria, persistent epigastric pain and/or vomiting, neurological symptoms such as hyperreflexia, severe frontal headache, visual disturbance or blindness, foetal distress and foetal intrauterine growth restriction (Pipkin

1995, Longo et al 2003, Sibai et al 2005). HELLP syndrome is a special type of severe pre-eclampsia which is characterized by hemolysis, elevated liver enzyme levels and a low platelet count. It is associated with the high maternal and perinatal morbidity (Longo et al 2003, Sibai et al 2005).

3.8.5 Mortality and morbidity of pre-eclampsia

Pre-eclampsia causes important maternal and perinatal morbidity and mortality (Roberts and Cooper 2001, Roberts and Lain 2002, Duley 2003, Sibai et al 2005). Maternal and perinatal complications in pre-eclampsia are usually determined by one or more factors including gestational age at onset of pre-eclampsia and time of delivery, the severity of the disease (multi-organ involvement of the disease), the presence of multi-foetal gestation, the presence of preexisting medical conditions and quality of management.

Perinatal death rate, percentage of preterm delivery, small-for-gestational-age infants and abruptio placentae are similar to those of normotensive pregnancies in women with mild pre-eclampsia. However, perinatal mortality and morbidities and the rates of abruptio placentae are substantially increased in women with severe pre-eclampsia (please see table 3.3), together with increased rate of caesarean section, mainly due to increased rates of induction of labour (Sibai 2003). Preeclamptic patients may also have a marked risk of sleep-disordered breathing due to UA narrowing probably caused by pharyngolaryngeal oedema (Pipkin 1995, Edwards et al 2000b).

Table 3.3 Maternal and foetal complications in severe pre-eclampsia (*From Sibai. Lancet 2005; 365(9461): 785-799*)

Maternal complications	**Neonatal complications**
●Abruptio placentae (1–4%) ●Disseminated coagulopathy/HELLP syndrome (10–20%) ●Pulmonary oedema/aspiration (2–5%) ●Acute renal failure (1–5%) ●Eclampsia (<1%) ●Liver failure or haemorrhage (<1%) ●Stroke (rare) ●Death (rare) ●Long-term cardiovascular morbidity	●Preterm delivery (15–67%) ●Fetal growth restriction (10–25%) ●Hypoxia-neurologic injury (<1%) ●Perinatal death (1–2%) ●Long-term cardiovascular morbidity associated with low birthweight (foetal origin of adult disease)

3.8.6 Prevention of pre-eclampsia

Protein or salt restriction, low-dose aspirin, oral calcium supplementation, fish-oil supplementation and other sources of fatty acids, zinc and magnesium supplementation and the use of diuretics and other antihypertensive drugs have been demonstrated to be unsuccessful or have a minimum benefit in preventing pre-eclampsia (Pipkin 1995, Longo et al 2003, Sibai 2003, Sibai et al 2005). There is some evidence that antioxidants such as vitamins C and E (Longo et al 2003, Sibai 2003, Sibai et al 2005) or heparin (Sibai et al 2005) may be beneficial, but there is insufficient evidence to recommend them.

Early diagnosis and treatment of sleep-disordered breathing in pregnant women might help to prevent the development of pre-eclampsia and intrauterine growth retardation (Charbonneau et al 1991, Lefcourt and Rodis 1996, Guilleminault et al 2004). Thus pregnant women, especially those with obvious predisposing factors, e.g. obesity, could

be screened for the symptoms of sleep-disordered breathing such as snoring (Edwards et al 2001, Edwards et al 2005). There is however no good evidence that CPAP is justified in the prevention or treatment of pre-eclampsia.

3.8.7 Management of Preeclampsia

The management of pre-eclampsia depends on foetal gestational age, foetal status, and severity of maternal condition at time of assessment.

●**Treatment of hypertension:** Treatment of acute hypertension stops potential cerebrovascular and cardiovascular complications (Longo et al 2003, Sibai et al 2005). The reduction of severe hypertension is necessary to prevent the risk of cerebrovascular complications such as further seizures. Parenteral hydralazine, labetalol, and short-acting oral nifedipine can be used to control acute severe hypertension in women with pre-eclampsia (Longo et al 2003, Sibai et al 2005).

●**Corticosteroids:** Corticosteroids improve pregnancy outcomes in women with severe pre-eclampsia or HELLP syndrome. Corticosteroid also can reduce the risks of neonatal intraventricular haemorrhage, infection, neonatal death and accelerate foetal lung maturity (Pipkin 1995, Longo et al 2003, Sibai 2003, Sibai et al 2005).

●**Delivery:** The definitive treatment of pre-eclampsia is delivery for mother, particularly those with severe pre-eclampsia. However, preterm delivery may be dangerous for the foetus, especially at under 34 weeks' gestation (Duley 2003).

3.8.8 Mechanisms of Disease: pathways of Sleep-disordered breathing and pre-eclampsia

Most pre-eclamptic women have common oedema which affects the entire UA and decreases UA calibre from nose to trachea due to differential soft tissue deposition in the neck. In addition to oedema, hyperemia, hypersecretion and rhinitis of pregnancy (which are due to increased oestrogen and progesterone levels) can cause nasal congestion. Increased nasopharyngeal resistance may make the airway pressure more negative during inspiration and contribute to the collapse of the pharyngeal airway during sleep.

Hyperventilation due to increased progesterone levels decreases levels of arterial carbon dioxide tension ($PaCO_2$). This could potentially induce periodic breathing at sleep onset which has been shown to contribute to sleep-disordered breathing. Increased progesterone levels also increase a diaphragmatic effort which leads to greater negative inspiratory pressures without increasing the UA muscle activities. This causes ventilatory instability which may increase the tendency for the airway to collapse during sleep.

A reduction in lung volumes, particularly FRC due to weight gain and displacement of the diaphragm and thorax can indirectly contribute to UA narrowing by reflex mechanisms. Decreased FRC will give one more profound hypoxemia during UA obstruction.

Weight gain during pregnancy or high baseline BMI before pregnancy may also result in UA narrowing because of increased fat deposition in the soft tissue of UA and possibly also external compression from fat masses.

As the prevalence of habitual snoring is higher in pre-eclamptic women than nonpregnant and pregnant women in third trimester of pregnancy, these hormonal and physiological changes may be quite severe in pre-eclamptic women and lead to an increase in upper airway resistance. These respiratory events may cause hypoxia/reperfusion which may contribute to the maternal vascular endothelium dysfunction.

Pre-eclampsia is characterized by widespread endothelial dysfunction throughout the maternal circulation resulting in hypertension. The specific factors initiating endothelial damage in pre-eclamptic are unknown. However, there is increasing evidence that pre-eclampsia is associated with increased oxidative stress due to both placental and maternal hypoxia/reperfusion. Oxidative stress occurs due to an imbalance between ROS and antioxidants. The generation of ROS leads to lipid peroxidation and subsequent endothelial cell injury, which can cause the maternal manifestations of pre-eclampsia.

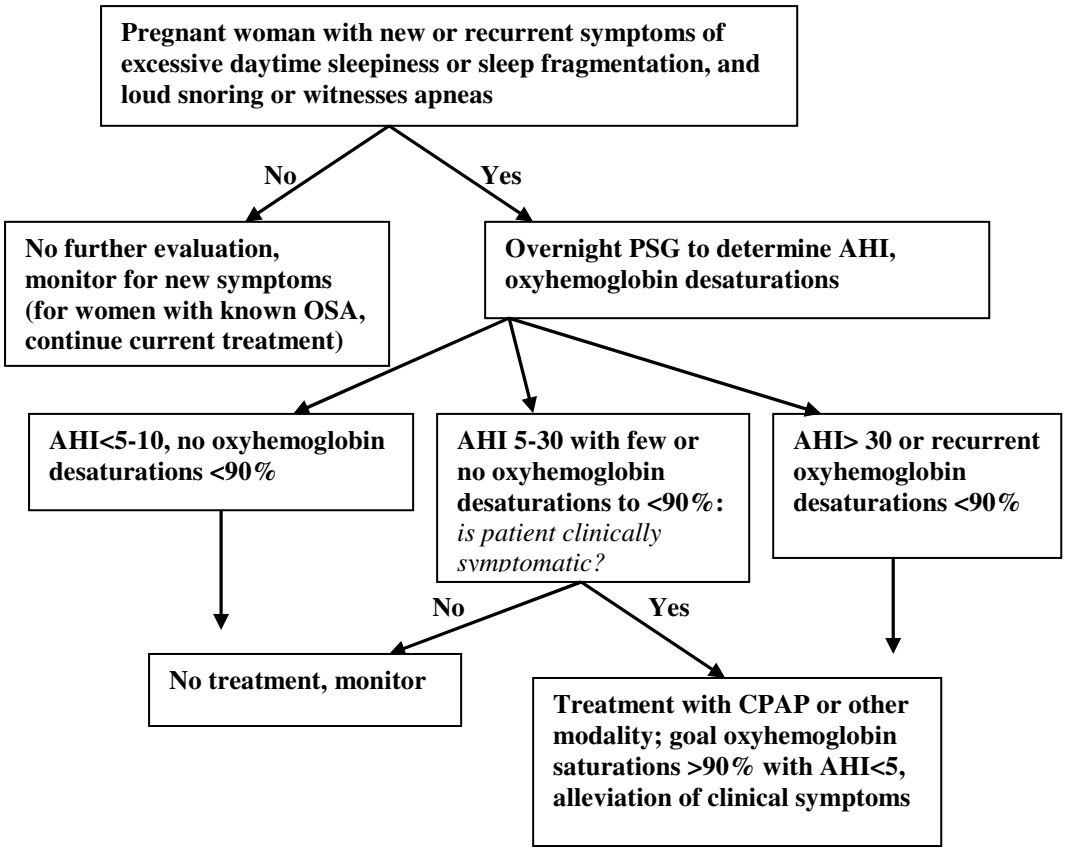
Vascular endothelium dysfunction and oxidative stress are also associated with sleep-disordered breathing. The hyperoxia, hypoxia, and oxygen free radicals may cause damage to endothelial and vascular smooth muscle cells. Thus, endothelial dysfunction may lead to the abnormal regulation of blood-vessel tone, peripheral vasoconstriction, potentially hypertension and adverse cardiovascular outcome. However, there is accumulating evidence of impaired vascular function, impaired endothelium function and altered oxidative status (Foster et al. 2007), but the relationship of these factors is not clear.

Endothelial dysfunction in pre-eclamptic women may lead to intrauterine growth retardation and other maternal manifestations of pre-eclampsia in addition to high blood pressure. Therefore one can speculate that maternal hypoxia/reperfusion, due sleep disordered breathing, may exacerbate pre-eclampsia due to increasing the severity of endothelium dysfunction. In fact, a recent study by Yinon et al (2006) reported that both sleep-disordered-breathing and endothelial dysfunction occur more often in women with pre-eclampsia than in women with uncomplicated pregnancies.

3.9 How should pregnant women be evaluated for symptoms of sleep-disordered breathing?

There is currently no consensus on the evaluation and treatment of sleep-disordered breathing in pregnancy in patients with or without pre-eclampsia. However, Pien and Schwab (2004) suggested some recommendations in a review article for pregnant women suspected of having OSAHS which is presented in figure 3.1.

Figure 3.1 Recommendations for pregnant women suspected of having obstructive sleep apnea. (*From Pien et al. Sleep 2004; 27(7): 1405-17).*



The cornerstones of the evaluation process include careful history and examination. Symptoms of sleep-disordered breathing: snoring, witnessed apnoea and excessive sleepiness can be monitored during pregnancy. Furthermore, factors predisposing to sleep-disordered breathing can be examined in pregnant women such as UA abnormalities and large neck circumference as well as obesity (Edwards et al 2005). Women who do not have sleep-disordered breathing before pregnancy, but have risk factors for sleep-disordered breathing, may require careful surveillance during pregnancy in order to detect the precipitation of sleep-disordered breathing since sleep-disordered breathing may likely develop, when pregnancy progresses (Guilleminault et al 2004).

Guilleminault et al reported that physical examination revealed abnormal oropharyngeal anatomy with a small oropharynx in 12 pregnant women with OSAHS diagnosed, 7 prior to pregnancy and 5 early in their first trimester (Guilleminault et al 2004).

Pien and Schwab (2004) et al suggest (fig 3.1) that pregnant woman with new or recurrent symptoms of excessive daytime sleepiness or sleep fragmentation and loud snoring or witnessed apnoeas should undergo an overnight PSG to determine AHI and oxyhemoglobin desaturations. If a woman has one of the following conditions: (1) an AHI 5-30 with few oxyhemoglobin desaturations <90% and clinical symptoms or (2) AHI>30 or (3) recurrent oxyhemoglobin desaturations <90%, she should be treated with CPAP or other treatments. The main aim of these treatments is to obtain oxyhemoglobin saturations >90% with AHI<5 and alleviation of clinical symptoms. However this treatment plan is not evidence based.

Pregnant women with known sleep-disordered breathing prior to pregnancy can continue their current treatment (Pien and Schwab 2004). However, the condition may need to be reassessed, particularly in the third trimester of their pregnancy, because the severity of the disease can be exacerbated with weight gain (Edwards et al 2005).

Currently, PSG is not recommended for simple snoring, pre-eclampsia, or intrauterine growth retardation (Pien and Schwab 2004). Therefore, except for patients with obvious signs and symptoms of OSA, patients with mild to moderate sleep-disordered breathing may be under-diagnosed in the pregnant population.

3.10 Who should be treated for sleep-disordered breathing?

In all pregnant women, general measures, such as avoidance of excessive weight gain and sleeping in a supine position, can prevent sleep-disordered breathing (Trakada et al 2003). Pregnant women with position-dependent apnoea/hypopnoea (without significant oxyhemoglobin desaturations or hypertensive complications) may possibly benefit from sleeping in the lateral decubitus position (Pien and Schwab 2004, Trakada et al 2003). Overweight women considering pregnancy should be informed about the risks of obesity in pregnancy and recommended to lose weight before pregnancy in order improve their health and to decrease the risk of sleep-disordered breathing during pregnancy.

CPAP has been successfully used on pregnant women with OSAHS and severe dyspnoeic attacks (Conti et al 1988, Kowall et al 1989, Charbonneau et al 1991, Polo and Ekholm 1995, Lewis et al 1998, Guilleminault et al 2004). CPAP pressure may require re-adjustment due to weight gain during pregnancy. For example, in a study of 12 pregnant females diagnosed with UARS or OSAHS in early pregnancy, 6 of them needed an increase in CPAP pressure at 6 months gestation. The adherence to CPAP treatment was very good at >80%. Home monitoring during the eighth month of gestation demonstrated normal SaO_2 during sleep and absence of apnoea, hypopnoea and tachypnoea (Guilleminault et al 2004).

CPAP has also been used in several studies of women with pre-eclampsia. In the first study of 11 pre-eclamptic women, CPAP abolished inspiratory airflow limitation, significantly reduced nocturnal blood pressure and improved nocturnal oxygenation (Edwards et al 2000b). However, this study had limitations. There was no control group,

treatment and non-treatment nights were not randomized and daytime blood pressure was not measured to determine whether the effect of CPAP was continued (Edwards et al 2000b). In a second study which is a randomized controlled trial of nasal CPAP of 24 women with severe pre-eclampsia, the data indicated that sleep is associated with adverse hemodynamic changes (heart rate, stroke volume, and cardiac output, mean arterial pressure) in pre-eclampsia. In this study there was not true randomization, but every second subject was allocated to receive the treatment. The use of nocturnal nasal CPAP in women with pre-eclampsia was associated with a decrease in mean arterial pressure by 3 mmHg from wakefulness to sleep compared with the change during night without CPAP, and with reversal of the decrease in cardiac output during sleep (a reduction of only 0.13±1.3 L/min, from wakefulness to sleep compared with the change during night without CPAP - 2±0.7 L/min). Improving cardiac output and mean arterial pressure during sleep may reduce the risk of intrauterine growth retardation associated with pre-eclampsia (Blyton et al 2004).

This evidence suggests that CPAP cannot treat the underlying cause of pre-eclampsia, but decreases blood pressure and thus potentially allowing the pregnancy to proceed for longer thus ensuring greater foetal maturity at delivery. However, results of these studies should be interpreted carefully due to the limitation of the studies. Therefore CPAP use in the treatment of pre-eclampsia should not be recommended at present.

Supplemental O_2 may possibly be considered for pregnant women who are unable to use more effective therapies such as CPAP.

Tracheostomy has been performed in a pregnant woman with OSAHS, but the case is an unusual example of tracheostomy during pregnancy (Hastie et al 1989). It is generally used for severely compromised cases.

3.11 The management of pregnancy-associated sleep-disordered breathing after delivery

It has been reported that sleep-disordered breathing subsides after delivery (Kowall et al 1989, Hertz et al 1992, Guilleminault et al 2000, Trakada et al 2003, Edwards et al 2005). Thus, a postpartum PSG can be necessary after weight stabilization (eg, ≥3 months postpartum) to detect whether sleep-disordered breathing persists in women.

Pien and Schwab (2004) provide some postpartum recommendations for women with pregnancy-associated sleep apnoea in their review article (table 3.4). These recommendations can be considered in the management of pregnancy-associated OSAHS after delivery.

Table 3.4 Postpartum Recommendations for women with pregnancy-associated sleep apnoea (*From Pien and Schwab Sleep 2004; 27(7): 1405-17)*

	Initial Postpartum Management	**If Symptoms Recur with Withdrawal of Therapy, or Weight Gain Persists**
Mild to moderate pregnancy-associated sleep apnea	Postpartum withdrawal of therapy with close follow-up for symptom recurrence; if asymptomatic, monitor for recurrence in future pregnancies	Obtain overnight PSG to determine baseline AHI; assess need for treatment and therapeutic options based on findings
Severe pregnancy associated sleep apnea	Continue therapy and obtain overnight PSG when weight within 10% to 15% of baseline to rule out persistent OSA	Obtain repeat overnight PSG to establish baseline AHI (consider split-night study with CPAP titration) and need for continued therapy
Preexisting sleep apnea	Consider return to prepregnancy therapy when weight within 10% to 15% of baseline, with close follow-up for symptom recurrence	Repeat overnight PSG (with split-night study if using CPAP at baseline) to determine new baseline AHI; modify prepregnancy therapy based on findings

3.12 Summary

Symptoms of sleep-disordered breathing are common among pregnant women due to pregnancy-related changes in the respiratory system. Sleep-disordered breathing in pregnancy is associated with maternal-foetal complications, including pre-eclampsia and intrauterine growth retardation. Placental hypoxia/reperfusion may play an important role in the pathophysiology of pre-eclampsia. Clinical predictors of sleep-disordered breathing need to be established in pregnant women. Screening by sleep questionnaire during routine patients' visits may help to detect possible sleep disorders in pregnant women. Pregnant woman with loud snoring or witnessed apnoeas or recurrent

symptoms of excessive daytime sleepiness or sleep fragmentation might be offered an overnight PSG. Guidelines for the treatment of pregnancy-associated sleep-disordered breathing need to be developed. CPAP is the most effective treatment of sleep-disordered breathing during pregnancy but the indications for therapy in pregnancy are unclear.

3.13 Aims of this thesis

Snoring is uncommon in women of childbearing age but 2 to 3 times more common in pregnant women, particularly in those with pre-eclampsia (Loube et al 1996, Edwards et al 2000b, Franklin et al 2000), when it is associated with foetal growth retardation (Franklin et al 2000). In general, snoring results from anatomical narrowing of the UA (Bradley et al 1986). I have therefore hypothesised that pregnancy was associated with UA narrowing and that this was more severe in patients with pre-eclampsia. I have also attempted to clarify whether any increase in UA narrowing in pregnant women with pre-eclampsia is a pre-existing anatomical variant or is due to a greater change in UA size in pregnancy.

The major objectives of this thesis therefore are:

1. To examine whether UA narrowing is greater in pre-eclamptic than pregnant and in pregnant than non-pregnant women.
2. To compare UA size in pregnant women who are snorers with non-snorers.
3. To compare UA dimensions in late pregnancy with the post-partum state.
4. To investigate whether sleep complaints and problems are associated with pregnancy.

CHAPTER 4
METHODS OF MEASUREMENT

4.1 Introduction

The overall aim of this thesis was to assess UA dimensions during the third trimester of pregnancy and after pregnancy in healthy pregnant and pre-eclamptic women compared with non-pregnant women, and to study the association of snoring and sleepiness in pregnancy. This was investigated in 3 studies:

1. The first study was conducted to determine the effect of pregnancy and pre-eclampsia on UA size. In this study we measured UA calibre in healthy non-pregnant women and in pregnant women, who were in similar age, height, and pre-pregnancy weight or BMI, with and without pre-eclampsia.
2. The second study was designed to compare UA dimensions in healthy non-pregnant women and in pregnant women, who were in similar age, height, and pre-pregnancy weight or BMI, and UA dimensions in late pregnancy with the post-partum state.
3. The third study examined whether sleep complaints and problems are associated with pregnancy.

In the first two studies a cross sectional design was used, and the second study was extended with a follow up post-partum of some of the pregnant women. Third study was a prospective questionnaire-based study. The designs of these studies were chosen for the following reasons. A cross-sectional study is performed over a short period of time which is suitable for working with pregnant and especially pre-eclamptic women who have many difficulties with availability and transport. A follow-up study after pregnancy strengthens the results to show the effect of pregnancy on UA size within individuals thus removing between subject variance in cross-sectional studies. Such a

design is not readily applied to a pre-pregnant and pregnant measurement of UA size as recruitment of a group highly likely to become pregnant in a given time window is difficult. A prospective questionnaire-based study regarding sleep complaints such as snoring provides data which can be averaged over a period of 1 to 3 months rather than the kind of data obtained by only a one or two night study, if objective methods are used. It also decreases recall bias.

This chapter describes the recruitment of subjects for these studies, and the techniques and questionnaires which were used in these studies to measure UA sizes and anthropometric variables, and to assess daytime sleepiness, frequency of snoring and breathing pauses.

Also described in this chapter are the studies determining the reliability (consistency of the instruments used) and validity (how accurate these instruments were) of acoustic reflectometry and the questionnaires which were employed for the thesis.

4.2 Study populations and recruitment

All healthy pregnant women and women with pre-eclampsia in their third trimester of pregnancy were recruited at the Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh. Apart from a small number, all were recruited by me following discussion with the supervising clinical team and all gave written informed consent to the studies (appendix A and B) which had the approval of the Lothian Research Ethics Committee (Reference LREC/2000/6/44).

4.2.1 Healthy pregnant subjects

Healthy pregnant women in the third trimester of their pregnancies attending the day assessment unit for their routine antenatal screening or admitted to the antenatal ward for reasons rather than pre-eclampsia and PIH (see exclusion criteria) were consecutively considered for participation in these studies. Potential subjects (both nulliparous and multiparous) were identified by checking their current medical condition from the diaries of day assessment unit and the antenatal ward, and the woman's case notes. They were also screened using a sleep-wake questionnaire and records of key medical history and baseline physical characteristics (appendix C and D). Fifty were recruited in the Simpson Memorial Maternity Pavilion in the Old Royal Infirmary, and the rest after the move to the New Royal Infirmary.

Pregnant subjects were recruited under the following criteria:

Inclusion criteria: Singleton pregnancies without any pre-existing illness, women aged between 18 and 42, gestational age: third trimester of pregnancy (28 weeks or more), living in Edinburgh.

Exclusion criteria: Suffering from sleep apnoea prior to pregnancy or other sleep disorders (i.e. periodic leg movement and insomnia), essential or gestational hypertension or pre-eclampsia, diabetes mellitus, severe respiratory diseases, severe asthma (which is difficult to define but is characterized by acute or subacute episodes of breathlessness, cough, wheezing, and chest tightness, or any combination of these symptoms, and is associated with airways obstruction) and influenza, pharyngitis or having steroid treatment for any reason or abnormal foetus, or morbid obesity prior to pregnancy.

All of the pregnant women recruited for UA studies were initially informed about the possibility of the follow-up study. At least 3 months after their delivery, the subjects were contacted by letter (see appendix E) to invite them to participate in the follow-up study (a sleep-wake questionnaire and its partner version -appendix C and F- were sent at the same time). This procedure is detailed in chapter 6 (please see section 6.2.1) If the women were pregnant again, they were excluded from the follow-up study.

4.2.2 Pre-eclamptic women

Pregnant women with pre-eclampsia in the third trimester of their pregnancies, who attended a high risk clinic or were admitted to the day assessment unit and the antenatal ward for further investigations, were consecutively considered for inclusion in these studies. Potential patients (both nulliparous and multipara) were screened by checking their current medical condition from the diaries of the day assessment unit, high risk clinic and the antenatal ward, and their medical history from their case notes, and by using a sleep-wake questionnaire and by recording key medical history and baseline physical characteristics (appendix C and D). Thirty-seven of them were recruited in the Simpson Memorial Maternity Pavilion in the Old Royal Infirmary, the rest (45 women) after moving to the New Royal Infirmary.

Entry criteria for pre-eclamptic women were as follows:

Inclusion Criteria: Singleton pregnancies with pre-eclampsia, women aged between 18 and 42, gestational age: third trimester of pregnancy (28 weeks or more) and living in Edinburgh. Pre-eclampsia was defined as the presence of a new hypertension (blood pressure > 140/90 or > +30/+15 from booking blood pressure) with proteinuria (> 0.3 g/24 hours).

Exclusion criteria: Suffering from sleep apnoea prior to pregnancy or other sleep disorders (i.e. periodic limb movement disorder, restless leg syndrome and insomnia etc.), essential hypertension, diabetes mellitus, severe respiratory diseases, severe asthma and influenza, pharyngitis and having steroid treatment for any reason or abnormal foetus, or being morbidly obese prior to pregnancy.

4.2.3 Non-pregnant control subjects

Non-pregnant women were randomly selected from advertisement respondents. An advertisement (see appendix G) was placed on different clinics' notice boards (i.e. respiratory, infertility, antenatal, postnatal, neonatal etc.) in the Royal Infirmary. Twenty-two different places including libraries, the University of Edinburgh sports centre, cafés and coffee shops, restaurants and food shops were willing to have a copy of the advertisement posted on their public notice boards. Additionally, I visited hospital staff in different clinics and provided more information for those who were interested in taking part in the study and sleep-wake questionnaires and partner's questionnaires (appendix H and I) with the stamped self-addressed envelope. Fifty of them were recruited in the Old Royal Infirmary, the rest after moving to the New Royal Infirmary. Subjects were recruited under the following criteria:

All recruited subjects gave written informed consent to be control subjects. They were screened using a sleep-wake questionnaire and recording key medical history and baseline physical characteristics (appendix H and J) and interview (through personal communication either face to face or on telephone).

Inclusion criteria: Aged between 18-45 and living in Edinburgh.

Exclusion criteria: Women suffering from sleep apnoea, or other sleep disorders (i.e. periodic limb movement disorder, restless leg syndrome and insomnia), hypertension, severe respiratory diseases, severe asthma and influenza, pharyngitis and having steroid treatment for any reason or being morbidly obese. Enrolled students of Edinburgh University were also excluded due to the requirements of Lothian Research Ethics Committee.

Control subjects were compared with pregnant women (both healthy pregnant and pre-eclamptic women) for age, height, and pre-pregnancy weight or BMI.
The procedures of the four studies and their subjects' characteristics are detailed in each chapter (see sections 5.2, 6.2, 7.2 and 8.2).

4.2.4 Subjects recruited for validity and reliability studies

In order to ensure that our results are valid and reliable, I recruited an additional 20 non-pregnant women (all hospital staff) using the same criteria used when recruiting non-pregnant women. They were between 22-41 years old, with a mean (SD) age of 33 (7) years. I administered the sleep-wake questionnaire (appendix H) and its partner version (appendix I), with a 30-day interval between the two tests, to them and their partners (11 partners were available). Additionally, the within-run reproducibility of acoustic reflectometry was studied in seven of these subjects, and day-to-day reproducibility of acoustic reflectometry was studied in twelve of them on three separate days over a 7-day period.

Eighty randomly selected UA measurements of non-pregnant women (from section 4.2.3) are also used for intra- and inter-rater reproducibility.

4.3 Data Collection

4.3.1 Upper-airway measurements

UA calibres in the awake state were measured using acoustic reflection technique described by Marshall et al (1993).

4.3.1.1 Acoustic reflection technique

It is a safe, non-radiating and non-invasive method that provides estimates of UA cross-sectional areas and lengths. The technique is based on the analysis of reflected sound waves from the airways generated by loudspeaker and recorded with a microphone and computer system. Measurements of the amplitudes of the reflections (echoes) and their times of arrival at the sensing microphone allow construction of a plot of airway area against the distance from the microphone (Fredberg et al 1980, Brooks et al 1984, Brooks et al 1989, Marshall et al 1993a).

This technique was originally reported and used in human beings by Fredberg et al (for details please see Fredberg et al 1980) and tested for accuracy and reproducibility (Fredberg et al 1980, Brooks et al 1984, Brooks et al 1989, Marshall et al 1993a). Although the principle remains the same, significant changes were made in the apparatus by other researchers (for details please see Brooks et al 1984, Brooks et al 1989, Marshall et al 1993a). The technique employed in this thesis has been modified by Marshall et al (incorporating improvements over previous systems) in several important aspects from those previously described (Fredberg et al 1980, Brooks et al 1984, Brooks et al 1989, Marshall et al 1993a). This modified reflectometer has three main advantages over the previous system: (1) it is much more compact and portable, (2) it allows free breathing during measurements (no need to equilibrate with helium/Oxygen), and (3) it

displays real-time plots of airway areas (Marshall et al 1993a). It was validated in detail (Marshall et al 1993a, Martin et al 1995, Martin et al 1997) and has been used successfully in previous studies in our Department (Jan et al 1994, Mathur and Douglas 1995b, Martin et al 1995, Martin et al 1997, Thurnheer et al 2001, Li et al 2005).

This technique has been used particularly for the comparative assessment of pharynx size among snorers, non-snorers, and patients with OSAHS (Bradley et al 1986, Martin et al 1995, Martin et al 1997, Mohsenin 2001, Thurnheer et al 2001, Li et al 2005). It has been shown to be a useful tool to discriminate changes in UA size with snoring, OSAHS, obesity, age and position (Bradley et al 1986, Martin et al 1995, Martin et al 1997, Mohsenin 2001).

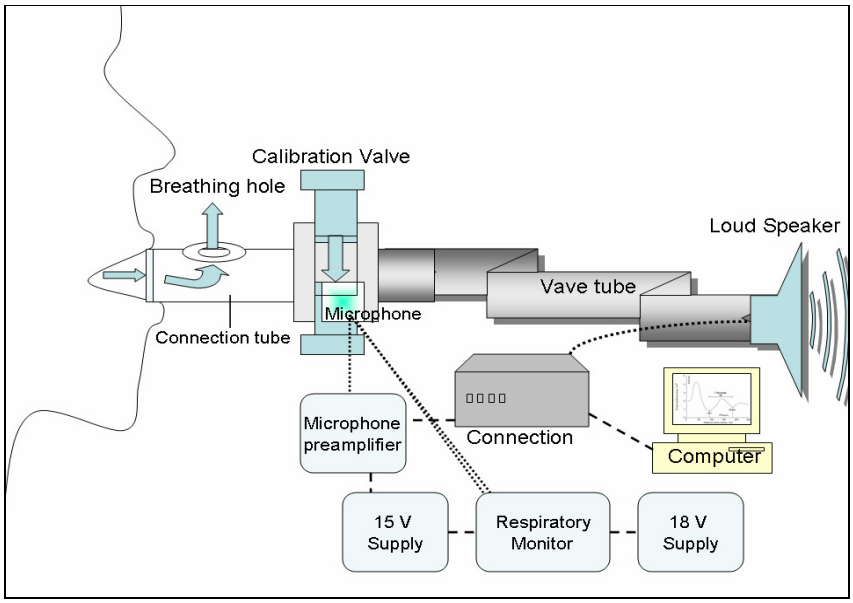
However, acoustic reflection can only measure UA size from the oropharynx and this requires deliberate oral breathing to ensure complete closure of the uvula to the posterior wall of the nasopharynx. This will stop acoustic waves transmitting to the nasal pathway. This technique cannot be used to assess nasopharynx because if applied by the nose there is first narrowing and then marked widening of the airway and the sound waves dissipate with luminal widening and so airway dimensions lower down cannot be measured. Thus this technique cannot be applied during sleep, when nasal breathing dominates, and cannot measure the retropalatal airway, which is often the site of the critical UA narrowing during sleep.

Equipment: The equipment (fig. 4.1) consists of a loudspeaker coupled to one end of a flexible wave tube (16 mm internal diameter flexible PVC tubing (Tygon 'Tygothane' from Norton Performance Plastics, Newcastle)), a pressure-sensitive microphone

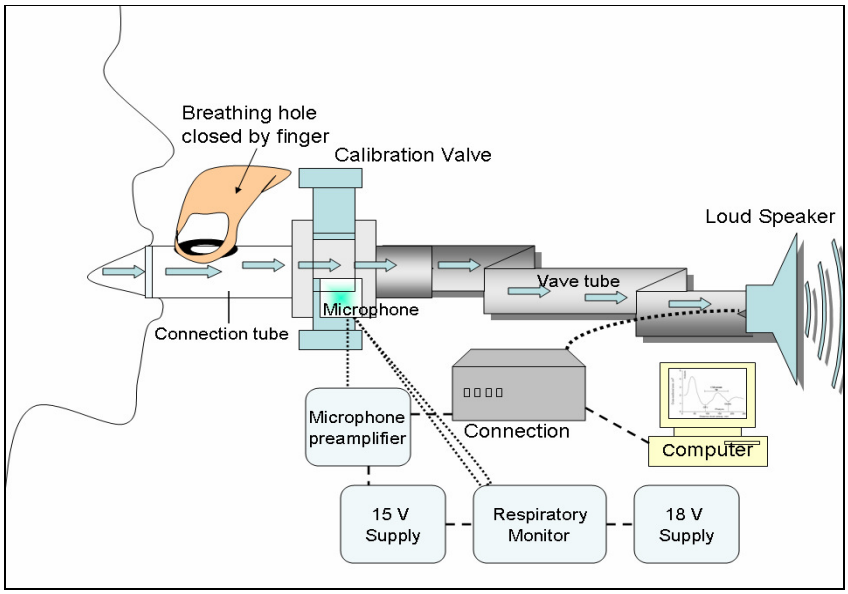
mounted in the wave tube wall near the distal end and a mouthpiece (Ohmeda, UK) attached, at the distal end of the connection tube (10 cm) with a breathing hole, to the subject. A calibration valve (fig. 4.1) just distal to the microphone allows the wave tube to be closed during calibration of the apparatus.

The subject is asked to close the breathing hole tightly with their finger during the UA measurements. This is to ensure that no spurious reflections occur. Additionally, the hole permits the subject to breath freely between measurements. The reflectometry is controlled by a 10 MHz 80286 (IBM AT-compatible) microcomputer, which drives the loudspeaker and collects the signal from the microphone preamplifier via a custom high-speed analogue interface card (fig. 4.1) (Marshall et al 1993a).

Figure 4.1 Apparatus used for acoustic reflectometry
a) A subject breathing via the breathing hole between two measurements

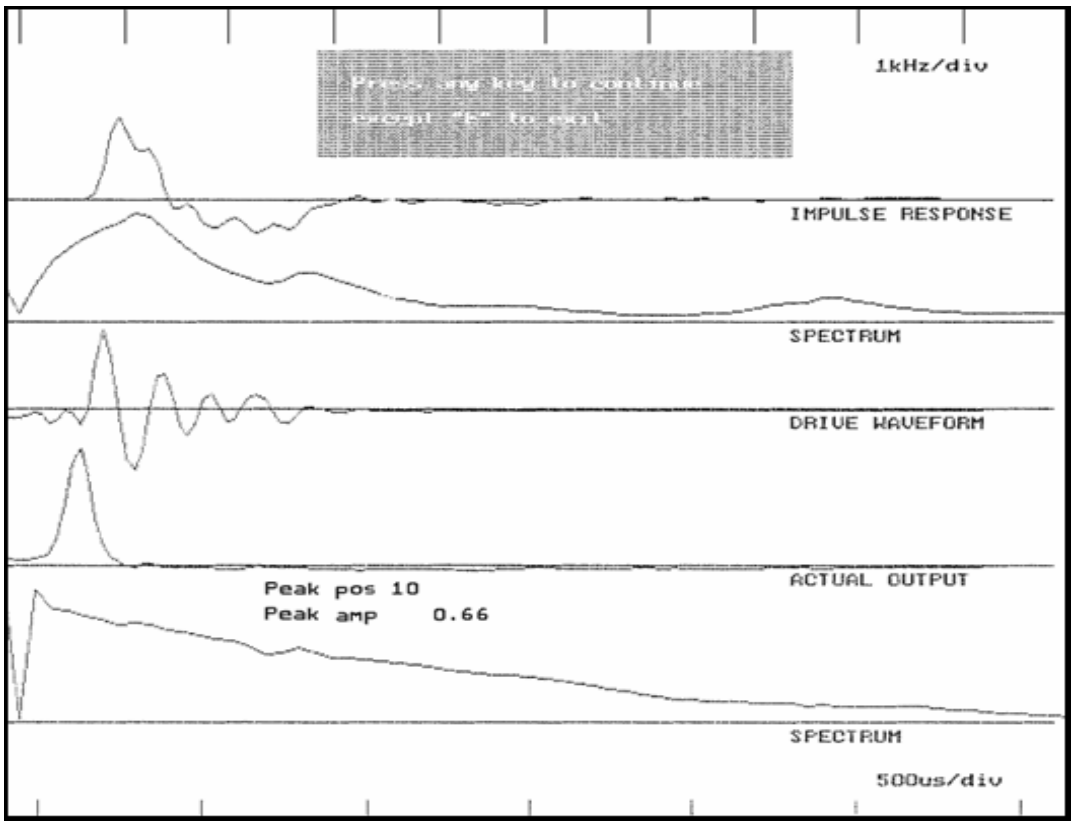


b) A subject during upper airway measurement



Calibration: The calibration of equipment is performed by closing the calibration valve (fig. 4.1) in order to occlude the source tube immediately beyond the microphone. The system then calibrates itself, measuring the impulse response of the loudspeaker/wave-tube/microphone combination. A screen display should appear which looks similar to figure 4.2.

Figure 4.2 Computer screen during calibration



Operation: With the calibration valve re-opened, the subject is coupled, via a mouthpiece, and measurement begins. Subjects breathe from the mouthpiece to acoustic reflection system after closing the breathing hole with their index finger. The computer excites the loudspeaker, and records the pressure wave. Separation, deconvolution and area reconstruction follow each excitation. The complete measurement, analysis and display cycle takes slightly less than one second, and so is 'real time'.

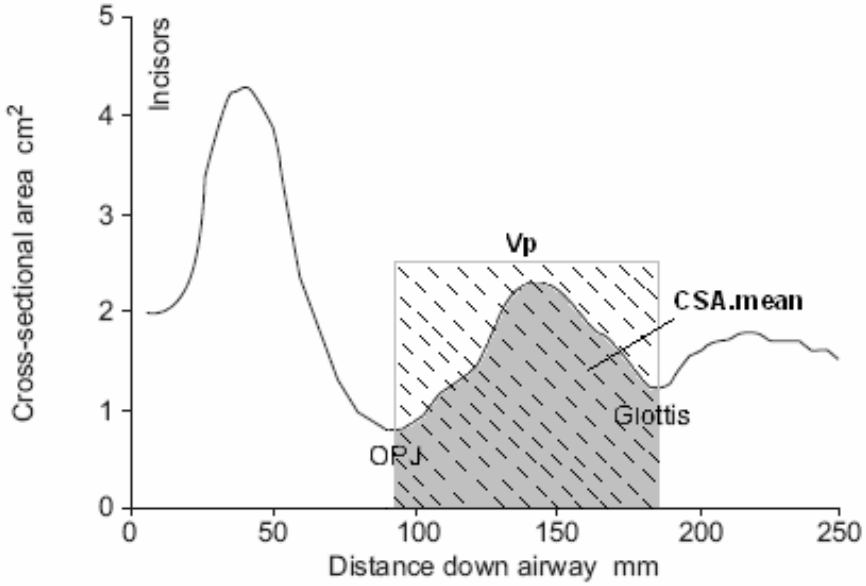
4.3.1.2 Anatomical landmarks recorded by acoustic reflectometry

A trace recorded by acoustic reflectometry (figure 4.3) demonstrates five anatomical points along the UA where areas or volumes are measured: oropharyngeal junction

(OPJ, the junction between the soft palate and the oropharynx; cm^2); maximum pharyngeal area (cm^2); glottis (cm^2); mean cross-sectional area from the OPJ to the glottis (CSA.mean; cm^2); and pharyngeal volume (Vp; cm^3) as the integrated area under the curve between the OPJ and the glottis. The mean pharyngeal area (CSA.mean) was obtained by integrating the area from OPJ to the glottis and dividing by the integrating distance (Brown et al 1986) as shown in the figure 4.3. Pharyngeal volume (Vp) was taken as the integrated area (Brooks et al 1989).

In this thesis, OPJ, mean cross-sectional area. and volume were selected due to our belief (when starting study) that they were reproducibile and accurate (Marshall et al 1993a, Martin et al 1995, Martin et al 1997), and the fact that they are sites of UA collapse in patients with sleep-disordered breathing (Hudgel 1986, Schwab et al 1993a, Schwab et al 1995, Isono et al 1997, Isono et al 2003, Schwab et al 2003).

Figure 4.3 Example plot of upper airway measurement produced by acoustic reflectance



Abbreviations: OPJ = oropharyngeal junction; CSA.mean = mean pharyngeal cross-sectional area; Vp = pharyngeal volume

Although maximum pharyngeal cross-sectional area is an easily identifiable point in an individual's UA measurements, this point was proved to be extremely variable in each person (Fredberg et al 1980, Brooks et al 1989). It was shown that acoustic reflectometry appeared to underestimate maximal hypopharyngeal areas by 35% compared with magnetic resonance imaging (MRI) estimates (Marshall et al 1993a). Fredberg et al (1980) reported that acoustic and radiographic measurements of the glottis showed great differences, probably due to the inappropriateness of the elliptical cross-section assumption in these regions. In contrast, acoustic measurement of mean pharyngeal cross-sectional area has been found to be a reproducible index of UA size with Coefficient of Variation expressed as a percentage (CV: 100 x SD divided by mean) of around 10% (Brooks et al 1989). Both pharyngeal mean cross-sectional area and OPJ have been used successfully to show differences between normal subjects, snorers, and those with OSAHS (Bradley et al 1986, Martin et al 1995). However pharyngeal volume, maximum pharyngeal area and glottic area did not differ significantly in the same study groups (Bradley et al 1986, Martin et al 1995). Marshall et al reported that the MRI and acoustic estimates of pharyngeal volumes were within 10% (Marshall et al 1993a).

4.3.1.3 Airway measurements with the phase of breathing

In an earlier version of acoustic reflectometry which is modified by Marshall et al (1993a,b), the breathing hole was closed by means of a sliding respiratory 'shutter' valve 100 ms before an airway measurement was to be made. The valve reopened 50 ms afterwards. A pressure transducer connected to the respiratory valve was used to monitor airway pressure at the mouthpiece end of the valve body. Pressure changes allowed the pressure transducer to detect respiration and synchronization of airway measurements with the phase of breathing. Electrical signals produced by the transducer

were amplified and compared with a reference level in order to detect the trigger point at which the computer briefly closes the respiratory valve and measures the airway area. However, the respiratory valve was found to be unreliable and was not fitted to later versions of the equipment (Personal communication with Dr. Marshall). Thus, the respiratory valve was not used in the studies in this thesis and airway measurement was not synchronised with the phase of breathing.

Marshall (1993b) studied the effect of respiratory phase on UA measurements in 9 volunteers. Subjects were seated with the head in a neutral position, and breathed quietly through a mouthpiece. The respiratory pressure developed in the mouthpiece was used to trigger measurements at either the start of inspiration or the start of expiration. There were no differences between areas measured during inspiration and expiration. One subject, however, had significant area differences with the respiratory phase, when breathing deeply between TLC and RV. Averaged over 11 breaths, the OPJ was 1.3±0.2 cm2 on deep inspiration and 1.9±0.3 cm2 on deep expiration ($p<0.001$). Brown et al (1986) also reported that pharyngeal area decreased from 35 to 12% in men and from 23 % to 9 % in women during expiration from TLC to RV. The results did not change after adjusting body surface area and vital capacity.

In our study, we assumed that respiratory phase would not make a difference. However we are not sure since we did not study it and our subjects were pre-eclamptic women who have UA problem. These women probably cannot activate their compensatory mechanisms like healthy individuals.

4.3.1.3 Physiological and technical factors contributing to the variability of measurements of acoustic reflection technique

Early studies addressed some technical issues regarding variability of UA measurements such as the mouthpiece, noseclips, the effect of soft palate position and neck flexion (Fredberg et al 1980, Rubinstein et al 1987, Brooks et al 1989, Marshall et al 1993a). The construction of the mouthpiece can be important, because their shape can affect UA measurements. In early studies, neoplex dental casting material, dental wax and commercial rubber mouthpiece were used (Fredberg et al 1980, Brooks et al 1989). Later, Rubinstein and Fredberg et al (1987) noted that measurements of UA area by acoustic reflections may be further simplified by using a scuba-diving mouthpiece without noseclips.

Marshall et al (1993a,b) investigated the effect of soft palate position (controlled by the mode of breathing) on cross-sectional area and found that UA measurements vary with the position of the soft palate. Oral breathing occurs with the nasopharynx closed off (fig 4.3); nasal breathing with soft palate closing off the back of the mouth (the total loss of the pharyngeal peak (OPJ to glottis)) and mixed oral/nasal breathing with the soft palate in an intermediate position (up to 2 cm^2 increases in any of the mouth, pharyngeal or glottic airway areas). The soft palate remains closed during tidal breathing only if a noseclip is not worn (Brooks et al 1984).

Rubinstein et al (1987) also studied the effect of neck flexion and extension on UA measurements and found that control of head position during measurements is not critical provided there is no obvious neck flexion.

UA estimates were made with a 'conventional' straight, rigid tube in previous studies (Fredberg et al 1980, Brooks et al 1984, Brooks et al 1989). However, Marshall et al (1993a,b) used a flexible wave tube because it allows for a much more compact and portable system, and provides a more convenient connection to the patient. They showed that UA measurements of the airway model made with the flexible wave tube were not significantly different from estimates made with a 'conventional' straight, rigid tube.

Marshall et al (1993a,b) also used disposable plastic mouthpiece (Ohmeda, UK) without noseclips in all volunteer studies to validate acoustic reflectometry because it is small, tolerated well by subjects, and produces reproducible measurements (Brooks et al 1989, Marshall et al 1993a,b, Martin et al 1997). I used the same equipment and followed the same practices as those used by Marshall et al (1993a,b) in all my studies, including the validation studies.

4.3.1.4 Accuracy and validation of the acoustic reflectometry

The accuracy and reproducibility of acoustic measurements of UA size have been documented in vitro (Brooks et al 1984, Marshall et al 1993a), in animal models (Brooks et al 1984) and in humans (Brooks et al 984, Marshall et al 1993a, Fredberg et al 1980, Brooks et al 1989).

●Validation studies with airway models: A perspex object with smoothly tapered internal diameters was used by Marshall et al (1993a, b) as a basic airway model to confirm that the flexible wave tube did not significantly degrade area estimations. The first airway model's maximal area of 6 cm^2 and 4 cm^2 represented the oral cavity and the

(hypo)pharynx respectively, whilst its minimum of 0.9 cm^2 represented the glottis. The second airway model had a greater oral cavity of 12 cm to investigate the effect of the mouth size on pharyngeal measurement. Validation of the reflectometer with these airway models gave accuracies and reproducibilities. The within-run and day-to-day reproducibilities (Coefficient of Variation) were 5% at the mouth and 10% at the pharynx and glottis (Marshall et al 1993a,b).

In an earlier study, cross-sectional area of in vitro airway models (glass airway models representing pharyngeal, laryngeal, and tracheal regions) was measured acoustically and roentgenographically. UA measurements estimated from acoustic reflectometry and roentgenograms agreed quite closely for small areas, but acoustic reflectometry underestimated roentgenographic estimates of area for larger UAs such as glottis, trachea by as much as 15% (Brooks et al 1984).

●**Animal studies:** Brooks et al (1984) qualitatively investigated the effects of airway wall rigidity by comparing acoustic and roentgenographic measurements of excised canine tracheae surrounded by either air or petroleum jelly. The UA measurement of air-surrounded excised tracheae by acoustic reflectometry underestimated roentgenographic areas by as much as 28% proximally. The accuracy of the UA measurements of these same tracheae surrounded by petroleum jelly was considerably improved and relatively independent of the distance along the trachea. Acoustic reflectometry uniformly overestimated roentgenographic areas by about 15% for distances beyond 3 cm.

Brooks et al (1984) speculated that differences in the accuracy of UA measurements of acoustic reflectometry in vitro and in vivo were probably due to differences in airway wall inertance.

●Human Studies: Earlier studies (Fredberg et al 1980, Brooks et al 1984, Brooks et al 1989) used helium/oxygen ($He/0_2$) gas to reduce the effects of non-ideal airway wall characteristics in human studies, but errors occurred with distance. This may be due to the fact that a $He/0_2$ gas mixture is more viscous than air. Marshall et al (1993a) used air in all human studies, as did we. It is much more convenient in clinical practice.

1. Reproducibility: Fredberg et al (1980) showed that there was good intra-subject agreement between acoustic and radiographic data of UA area. The average Coefficient of Variation was 16% for five trials in six subjects examining areas at the uvula, hypopharynx and glottis.

Earlier studies assessed the day-to-day variability of the Coefficient of Variation for ten subjects using a single mouthpiece on each of 3 different days (Brooks et al 1989, Brooks et al 1984). The mean intra-subject day-to-day variability of airway measurements by acoustic reflectometry was around 10% (Coefficient of Variation). Marshall (1993a) at al reported that the day-to-day Coefficient of Variation in five subjects on each of 21 days was 13±3% at the oropharyngeal minimum area and 11±3% at the hypopharyngeal maximum and glottal minimum areas.

The average of within-run Coefficient of Variation of airway area for acoustic-reflection measurement was reported to be 10 SD±4% (Brooks et al 1984) and 9% (range 3-18%)

(Brooks et al 1989) in ten subjects. These results were broadly confirmed by Marshall et al (1993a) that the within-run Coefficient of Variation for the pharyngeal area was 10%, identical to that reported by Brooks et al (1984). The standard deviation of the pharyngeal anatomical landmarks was approximately 0.2 cm^2 at the OPJ (2 cm^2) and 0.5 cm^2 at the hypopharyngeal maximum of 4.1 cm^2.

2. Comparison with MRI: In ten normal volunteers, acoustic and MRI methods were used to compare assessment of the pharyngeal and glottal areas. The results for the oropharynx were l.0±0.3 cm^2 acoustically and 0.9±0.5 cm^2 by MRI (p=0.77) with corresponding glottal areas of 1.3±0.3 cm^2 and 1.1±0.4 cm^2 (p=0.09) respectively (Marshall et al 1993a).

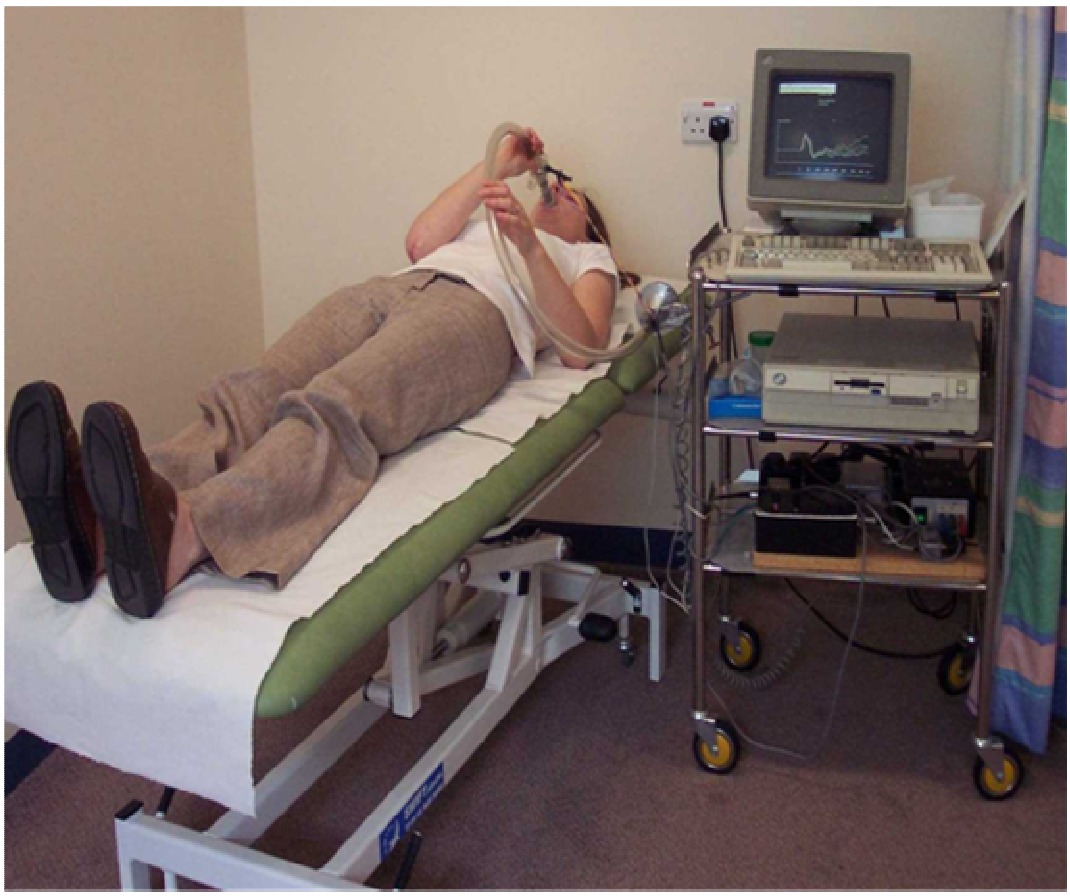
4.3.1.5 Protocol for upper airway measurements

Subjects were instructed to take their time and breathe normally (thereby avoiding problems associated with variability in lung volumes) through the mouth, without a noseclip, via a mouthpiece into a wave tube (Rubinstein et al 1987), so as to keep the nasopharynx occluded by the palate, thus preventing the loss of soundwaves into the nasal cavity. A standard curve of mouth peak, oropharyngeal minimum, pharyngeal peak and glottis minimum were screened in traces (fig. 4.3). If nasal breathing or mixed (oral/nasal) breathing (they were detailed above) were identified, the measurements were repeated, giving the same instructions to the subjects until satisfactory measurements made. All UA measurements were taken at FRC at the end of a normal expiration in the seated, supine (fig. 4.4) and the lateral recumbent positions. In the seated position, UA was measured while subjects were sitting on a straight-backed chair. The wave tube was placed horizontally, parallel to the ground. In the supine position

(fig. 4.4), subjects were completely flat without any pillows, and in the lateral position they were lying on their side with a pillow under their head to prevent neck flexion. Most of subjects were studied in the afternoon. This reduces the effect of circadian rhythms on UA muscle.

Five measurements were recorded at each testing. All measurements were stored onto a disk. These CSA-versus-distance-down-the-airway traces were anonymised and randomised, and scored in batches by the author who was blinded to case status. The author decided which traces were technically satisfactory, and averaged the results, deriving measurements of OPJ area, mean pharyngeal area and mean pharyngeal volume (see fig. 4.3) (Marshall et al 1993a, Martin et al 1995, Martin et al 1997).

Figure 4.4 Acoustic reflection technique used in this thesis



The traces were transferred from the Microsoft-Disk Operating System (MS-DOS) program to Microsoft Office Excel, to produce the same traces and obtain quantitative data. These data were then moved to SPSS for windows (Version 12, SPSS Inc., Chicago, IL, USA) and analysed using a variety of statistical tests which are explained in each chapter (chapters 5, 6 and 7).

4.3.1.6 Reproducibility of the scoring of acoustic reflectometry in this thesis

●The inter-rater and intra-rater comparisons: The main outcome measurements in chapter 5 and 6 in this thesis are UA dimensions. UA dimensions' scoring can be variable within and between scorers. To assess the accuracy of this scoring,

a. Forty randomly selected UA measurements of non-pregnant women (subjects' recruitment was detailed above) were scored by the researcher and compared with the scoring of a senior researcher.

b. A further 40 randomly selected UA measurements were scored twice by the researcher to assess reproducibility.

In these inter-rater and intra-rater analyses, both researchers were blind to the subjects' details and original results of the measurements. The interval between the first and second scoring of the same anonymised trace for intra-rater comparisons were ranged from 1 to 36 months after the initial measurements were scored.

Intraclass correlations coefficient (ICC) was used for the inter-rater and intra-rater comparisons because (1) it shows consistency of two measures of the same variable as

well as the relationship between two different variables, and (2) is sensitive to fluctuations in test scores. The results of the inter-rater and intra-rater studies are shown in table 4.1.

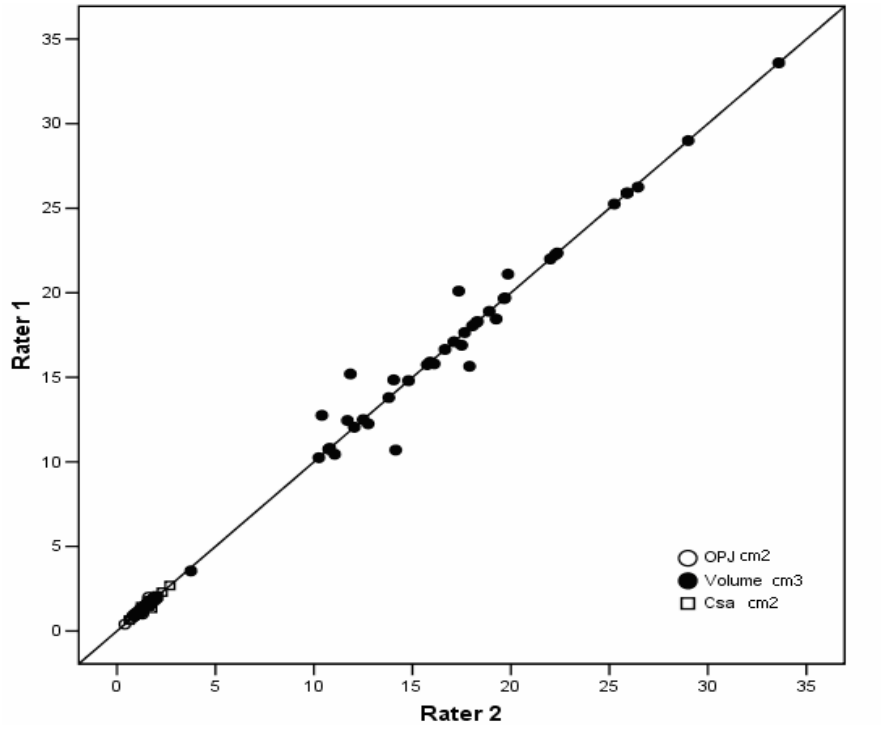
Table 4.1 The results of the inter-rater and intra-rater studies

	Score 1, mean (SD)	Score 2, mean (SD)	Intraclass correlation coefficient (ICC)	95% Confidence Interval
Inter-rater reproducibility				
OPJ cm^2	1.22(0.31)	1.20(0.29)	0.98**	0.96-0.99
VOL cm^3	17.40(5.87)	17.35(5.90)	0.99**	0.98-1
CSA cm^2	1.64(0.35)	1.64(0.36)	0.98**	0.97-0.99
Intra-rater reproducibility				
OPJ cm^2	1.21(0.29)	1.20(0.28)	0.98**	0.97-0.99
VOL cm^3	17.35(5.87)	17.27(5.77)	0.99**	0.98-1
CSA cm^2	1.64(0.35)	1.63(0.36)	0.98**	0.97-0.99

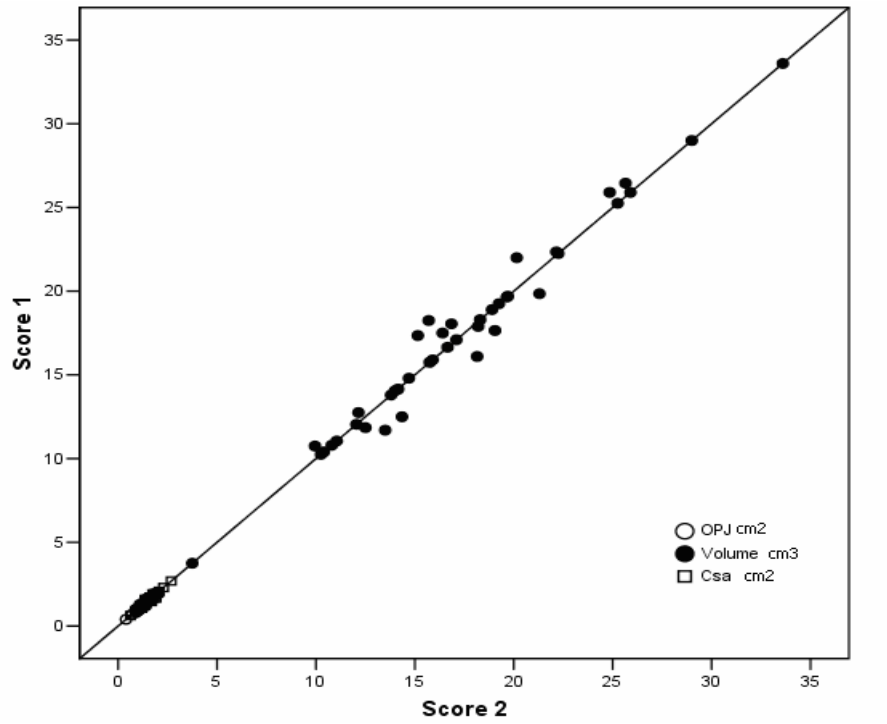
**$p< 0.001$

Figure 4.5 The inter-rater and intra-rater studies (scatter plots)

(a) Scatter plot of UA measurements between rater 1 and rater 2



(b) Scatter plot of UA measurements across 1st and 2nd scoring by the same rater

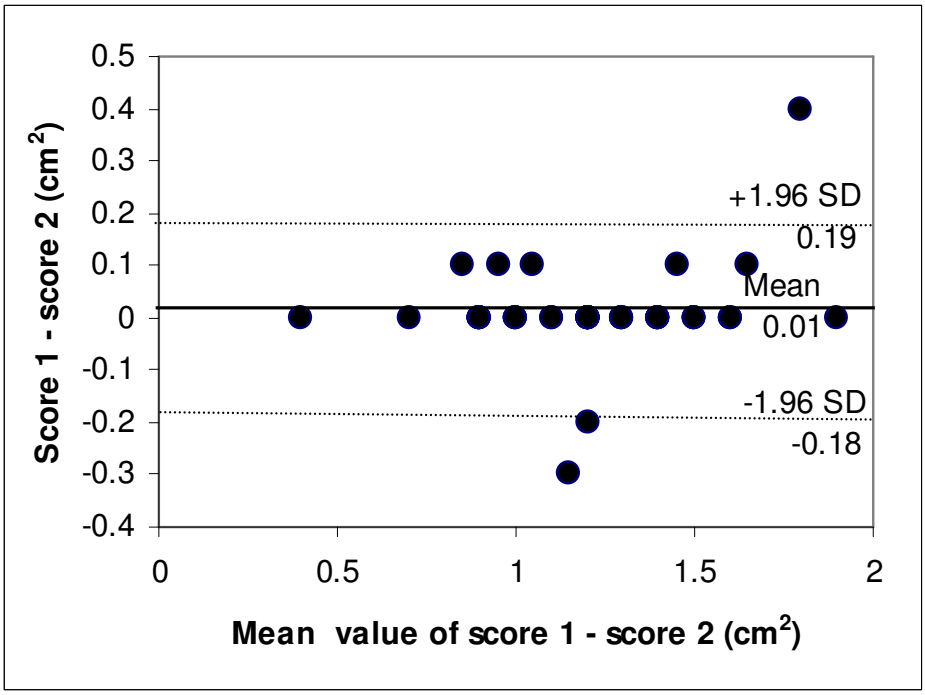


In this study, high ICCs ranged from 0.98 to 0.99 (Table 4.1) indicate that the intra-rater reproducibility and inter-rater reproducibility are very good.

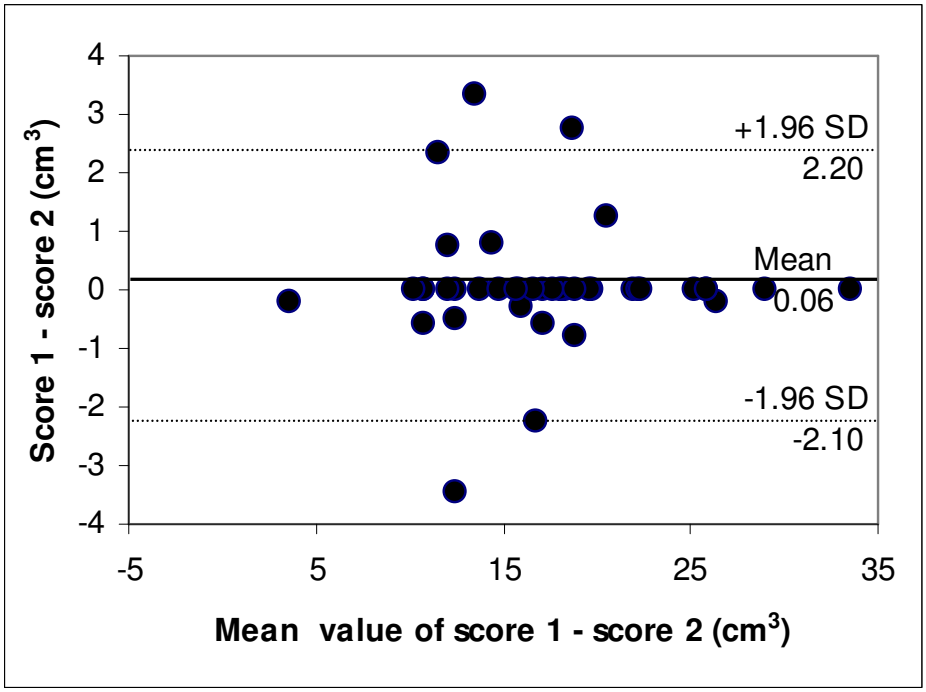
Bland-Altman plots were also performed for both intra- and inter-rater assessments. Bland and Altman (1986) suggested this alternative method for determining the agreement between two measurements which involved plotting the difference against the mean value of the two measurements.

Figure 4.6 Bland and Altman plots across 1st and 2nd scoring by the same rater

a) Opj



b) Pharyngeal volume



c) Cross-sectional area

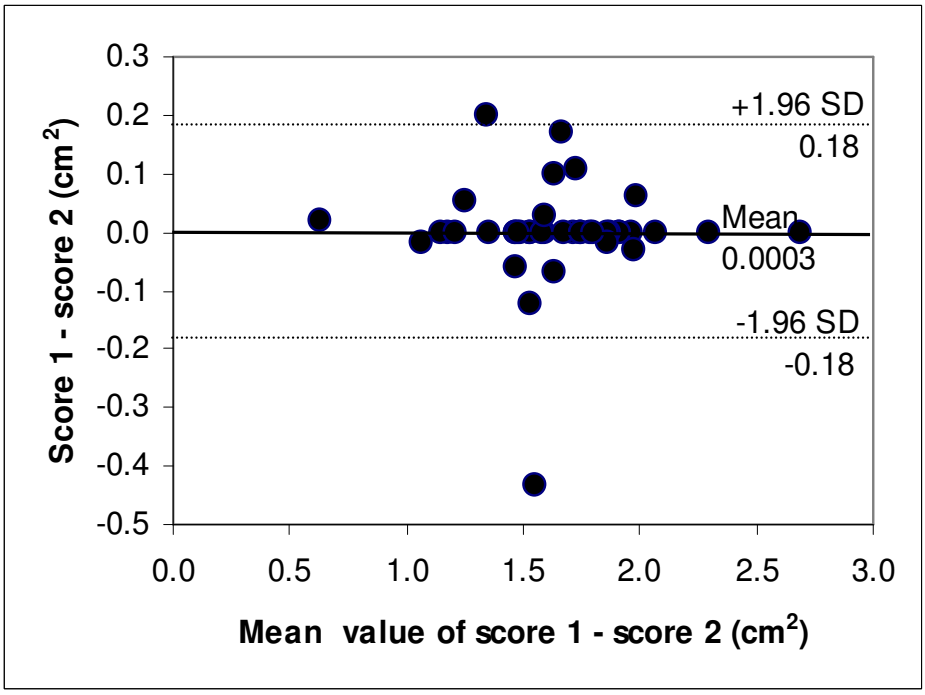
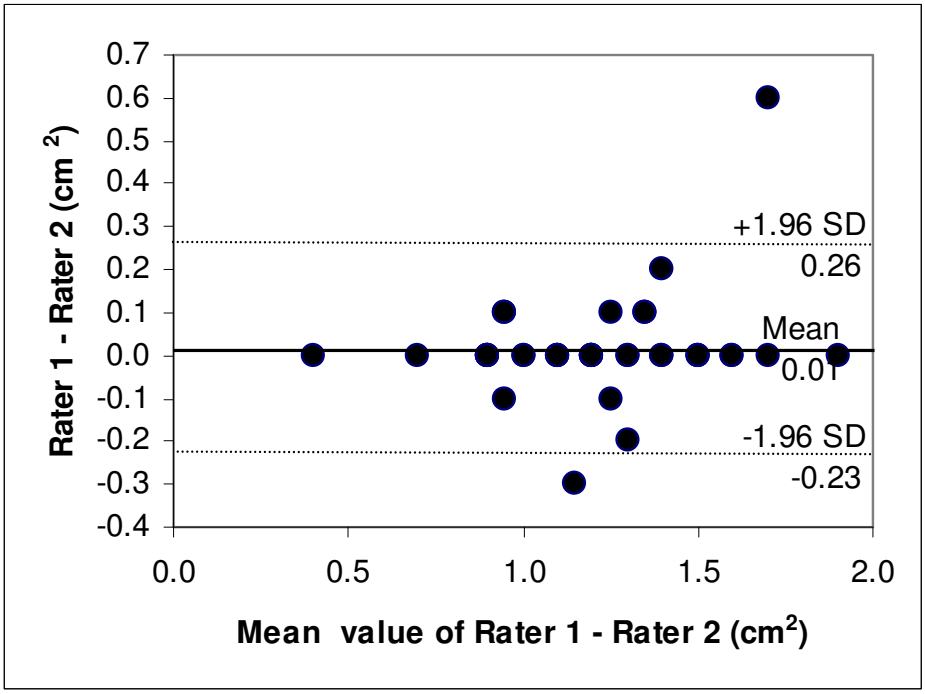
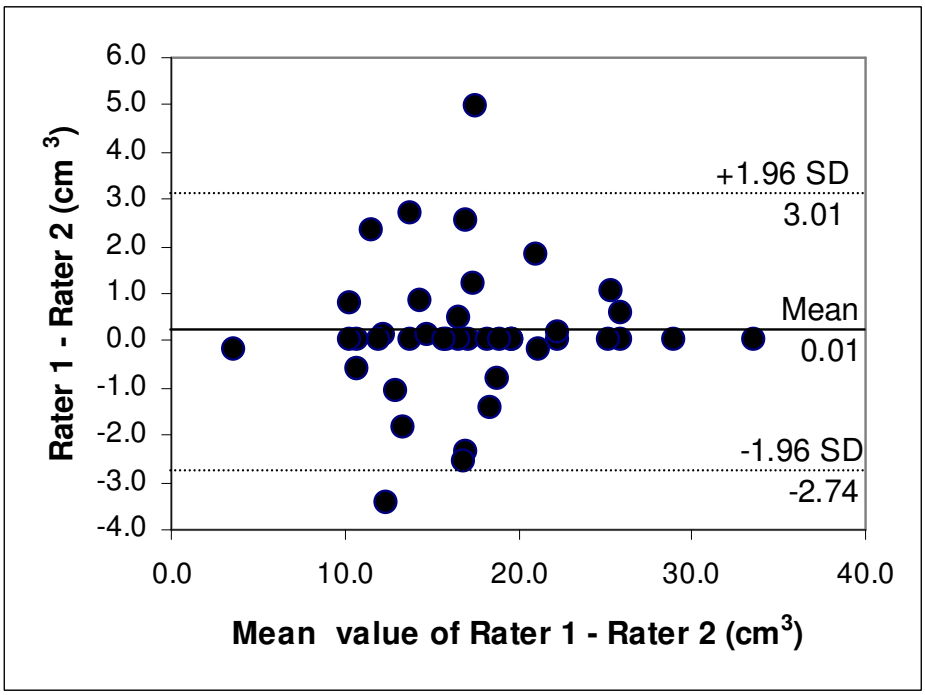


Figure 4.7 Bland and Altman plots across rater 1 and rater 2

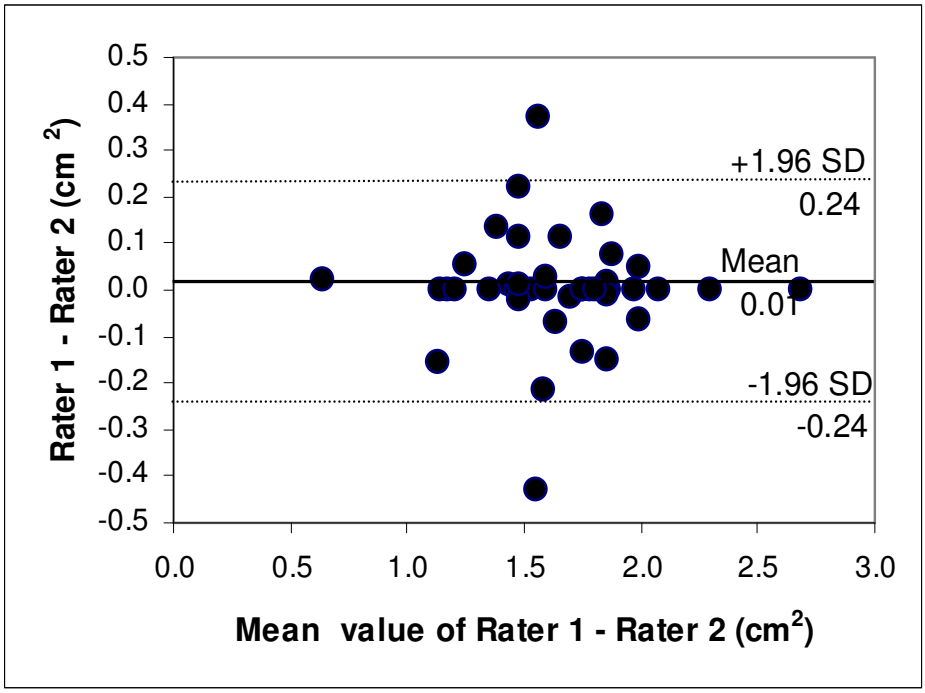
a) Opj



b) Pharyngeal volume



c) Cross-sectional Area



The inter-rater and intra-rater comparisons which are presented in figures 4.6-7 using Bland-Altman plots show that there is no significant difference across 1st and 2nd scoring by the same rater and also by two different raters.

●**Day to day reproducibility:** To assess day to day variability, I took 540 UA measurements from 12 non-pregnant women (who are detailed above) in three positions: seated, supine and lateral. These were obtained on three separate days over a 7-day period. I was blinded to the subjects' details and the order of days on which the measurements were taken.

The variability of UA measurements was calculated (Coefficient of Variation) for each subject. Day-to-day within subject variability was assessed for 540 UA measurements, 180 on each of 3 separate days (Table 4.2). Day-to-day variabilities of OPJ, pharyngeal

volume and mean cross-sectional area were 10±4%, 12±5, 8±3% in the seated position, 11±5, 14±4, 10±6% in the supine, and 11±5, 13±4, 11±4% in the lateral positions (Table 4.2).

These figures are similar to the 9±4% for mean cross-sectional area and 12% for pharyngeal volume reported by Brooks et al (1989, 1984) and 13±3% for OPJ by Marshall et al (1993a) in seated position. However, data regarding supine and lateral positions is previously unavailable, but our findings from the seated position demonstrate that measurements of UA dimensions by acoustic reflectometry are highly reproducible from day to day for women in reproductive age. The measured variations of 11-14% (in supine and lateral positions) are acceptable in a clinical physiological technique (Marshall et al 1993a).

Table 4.2 Day to day Variability of acoustic measurements of pharyngeal size

Subject No	Sit OPJ Cm^2	Sit Vol Cm^3	Sit CSA Cm^2	Sup OPJ Cm^2	Sup Vol Cm^3	Sup CSA Cm^2	Lat OPJ Cm^2	Lat Vol Cm^3	Lat CSA Cm^2
1	10	6	7	5	16	2	20	6	7
2	5	2	13	20	19	14	9	12	19
3	13	12	4	5	17	7	5	11	16
4	9	16	5	14	13	11	6	8	8
5	0	13	10	10	20	10	14	20	15
6	9	16	7	9	12	21	7	13	11
7	13	15	3	18	17	8	17	19	6
8	8	13	10	8	11	14	18	17	9
9	10	17	13	6	15	4	10	15	5
10	12	8	6	7	12	16	9	17	10
11	11	11	8	17	8	5	9	13	13
12	14	17	6	11	6	3	6	8	8
Mean (SD)	10(4)	12(5)	8(3)	11(5)	14(4)	10(6)	11(5)	13(4)	11(4)

No: subjects are numbered to prevent confusion

●**Within-run reproducibility:** A total of 70 UA measurements, 10 measurements from each subject at a single sitting, were taken to analyze within-run variability. Expressed as a Coefficient of Variation, within-run OPJ variability averaged over all subjects was 9%, volume was 12% and mean cross-sectional area was 11% (Table 4.3).

Table 4.3 Within-run variability of acoustic measurements of pharyngeal size in seated position

Subject No	OPJ Cm^2	Vp Cm^2	CSA.mean Cm^2
1	7	11	10
2	11	14	13
3	10	17	13
4	11	10	11
5	9	6	7
6	6	11	11
7	11	13	12
Mean(SD)	9 (2)	12(4)	11(2)

No: subjects are numbered to prevent confusion

Variations within a given subject may likely occur because of real physiological changes, or artefacts caused by extraneous noise or inconsistent breathing. However, these results show that UA measurements by acoustic reflectometry are accurate and reproducible.

4.3.2 Demographic measurements

Demographic measurements were measured by the author on all subjects: non-pregnant, pregnant and pre-eclamptic women including (1) date of birth, (2) body weight and body height for calculation of BMI (BMI = kg/m^2); (3) neck, waist and hip circumferences.

Neck, waist and hip circumferences were measured using a standard tailor's measuring tape. Neck circumference was determined in the seated position, at the level of the

superior border of the cricothyroid membrane. The waist was measured at the umbilicus, the hips were measured at the level of the iliac crests. Height (shoes off) was recorded from a standardised height bar. Weight (regular clothes) was measured using a standard medical scale (Seca). These measurements are documented in centimetres (cm) and kilograms (kg).

4.3.3 Blood pressure measurements

Blood pressure was recorded using a manual mercury sphygmomanometer (Accoson, made in UK). The measurement was taken after the woman had rested with no change of position for at least 5 minutes, in a sitting position. It was taken using the right arm which was placed at the level of her heart. To achieve this, her arm was raised or lowered on a comfortable support. Blood pressure was measured carefully to ensure that the cuff size is appropriate for each woman. A cuff was wrapped firmly but not tightly around the arm one inch above the elbow over the brachial artery. The unit was kept upright on a flat surface and the gauge read at eye level.

Whether to use Korotkoff sound 4 (muffling, K4) or 5 (disappearance, K5) when measuring diastolic blood pressure is a controversial question (Pipkin 1995). However, in practice at the Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, Korotkoff sound 4 is found to be practically more useful as disappearance of sounds often occurs at very low pressures in pregnancy. Therefore, Korotkoff sound 4 was taken as diastolic blood pressure in the studies in this thesis. These measurements are documented in mm Hg.

4.3.4 Records of key medical history and baseline physical characteristics

A sheet (appendix D) was filled out and numbered by the present author for each patient, which was used for these reasons:

1. Screening subjects
2. Recording demographic measurements and blood pressure
3. Backing up data (even though similar questions were asked in the questionnaire)

Some of the information was obtained from pregnant women's case notes such as expected delivery date. The questions regarding singleton/multiple pregnancy, gestational age, expected delivery date, pre-pregnancy weight etc. were asked only for pregnant women. The questions concerning whether they have Asthma, steroid treatment, sleep apnoea or other sleep disorders and sleeping position were asked of all subjects. The neck, waist and hip sizes, height, weight, and blood pressure were measured and recorded to this sheet. Additionally, notes were taken regarding recruitment criteria or issues which may affect the study's results.

4.4 Questionnaire assessments

Sleep wake questionnaire: A standard sleep-wake questionnaire (appendix C and H) and its partner versions (appendix F and I) were applied to all subjects and their partners. The questionnaire was applied at a convenient time, for pregnant women generally when they were waiting their turn in the waiting area in the day assessment unit for their monthly assessment or in the clinic for their treatment. A convenient time—either in their clinic (for hospital staff) or in the department of Sleep Medicine (for non-hospital staff)—was also sought for the control women. If the subjects had

limited time and their partners were not available during the study time, the questionnaires and self-addressed stamped envelops were provided for sending back the questionnaires. Fifty-pregnant women and their partners completed these questionnaires a second time at least three months after their delivery.

This questionnaire consisted of the following sections:

●**General questions:** General questions were asked to each subject including age, whether they have a regular bed partner, current occupation, and whether they do shift work/night work (yes/no), and if yes how long.

●**Questions on lifestyle habits:** We also assessed lifestyle habits such as smoking (tobacco/cigarette use/day and years), caffeinated drinks and alcohol consumption (drinks/week) and medications including sleeping pills (dose/day).

Subjects were classified as smokers if they were currently smoking tobacco/cigarettes, and as non-smokers if they had never smoked or as ex-smokers if they had smoked but had quit.

●**Questions on medical history:** Medical history was assessed by asking if they have had the following conditions or operations: asthma, hay fever, high blood pressure, stroke, nasal congestion, nose operations, throat operations, diabetes, thyroid problems, epilepsy, broken nose, depression /anxiety, chronic fatigue syndrome, or kidney /liver problems. The following events were also asked about: whether women have ever experienced, either in pregnancy or prior to becoming pregnant, hallucinations or vivid dreams whilst still conscious, paralysis or inability to move occurring at sleep onset or on awakening, muscular weakness or collapse whilst laughing or during strong emotion,

sensation of restlessness or crawling in their legs, bed-wetting (as an adult) or sleepwalking. The pregnant women were asked to emphasize whether the latter conditions occur either prior to pregnancy or during their pregnancies.

●Questions on sleep-related complaints: The questionnaire included some questions on sleep-related complaints: snoring and breathing pauses, snoring volume level and snoring position. These questions were posed in a format that allowed the subjects and their partners to retrospectively rate their response for the time before pregnancy as well as during the third trimester of pregnancy in order to assess alterations in women's sleep.

Snoring frequency and breathing pauses were rated on a five-point Likert scale, corresponding to 'never', 'rare' (1–2 nights per month), 'occasional' (1–2 nights per week), 'often' (3–4 nights per week), 'frequent or always' (more than 4 nights per week) and 'do not know'.

●Criteria for snoring and breathing pauses: For snoring and breathing pauses, the higher of the frequencies reported by the woman and partner was used. Snoring and breathing pauses were considered to exist in subjects if rated often or always. If they snored often or always (greater than or equal to 3 days per week), they were defined as habitual snorers.

●The test-retest reliability of the questions on sleep-related complaints in this thesis

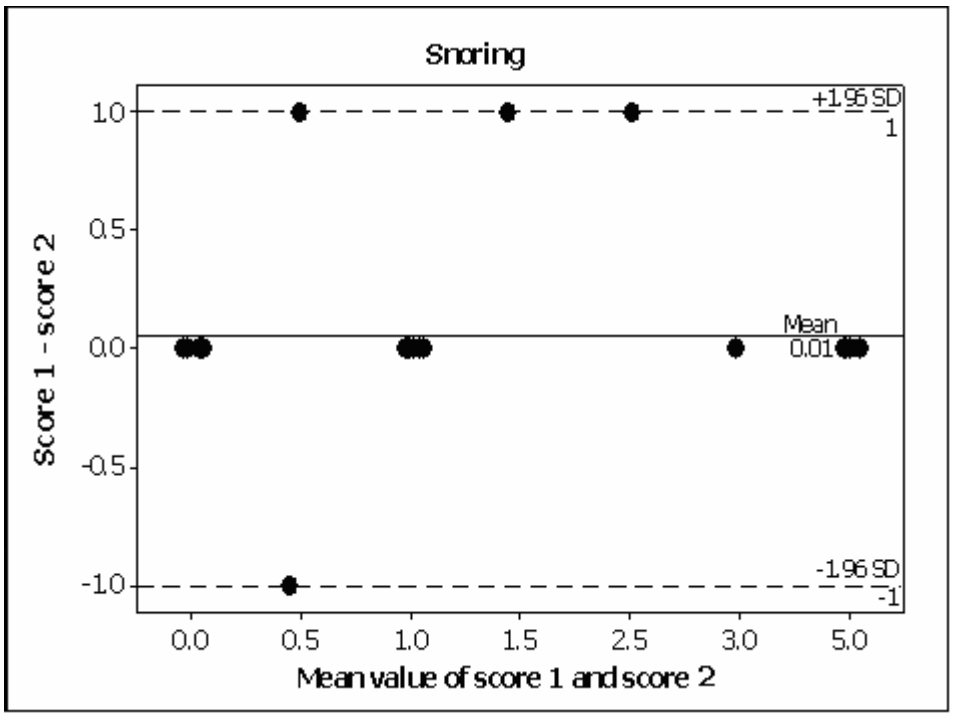
As mentioned above, these questions were asked to 20 non-pregnant women and their partners (11 partners) with a 30-day interval between the two occasions. The test-retest reliability coefficients (Spearman correlation) indicated a high level of reliability for the questions regarding snoring and breathing pauses, snoring volume level and snoring position (Table 4.4). Additionally, none of the Bland and Altman plots for each data set show any bias (see 4.8-9).

Table 4.4 The results of test-retest reliability of the questions on sleep-related complaints

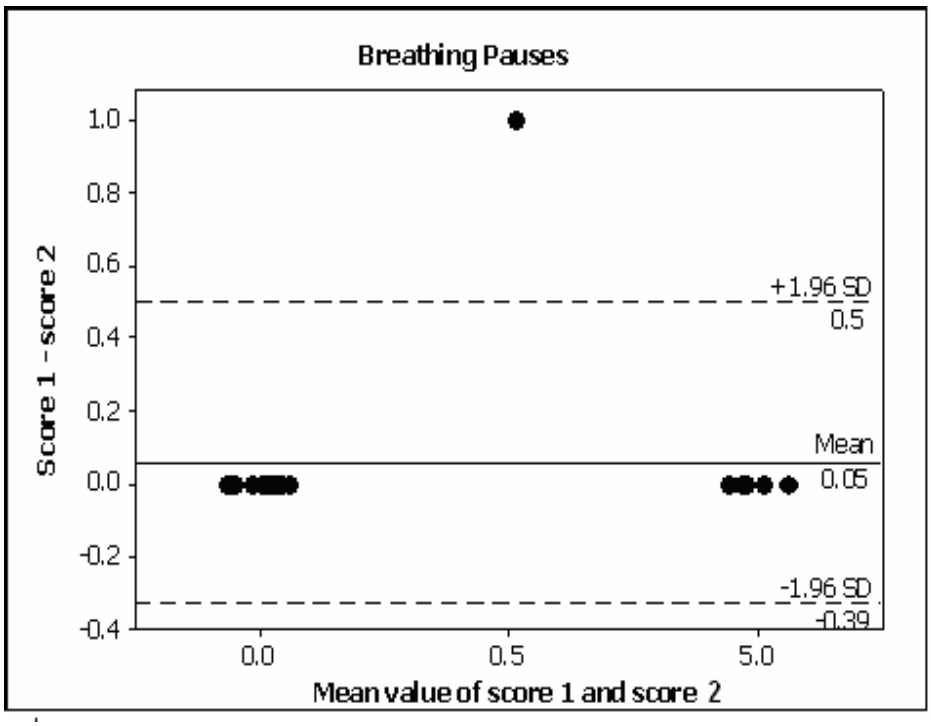
Questions	r	p
Snoring	0.91	0.01
Breathing pauses	0.94	0.01
Snoring volume level	0.89	0.01
Snoring position	0.88	0.01
Partner - Snoring	0.83	0.01
Partner - Breathing pauses	0.91	0.01
Partner - snoring volume level	0.99	0.01
Partner - snoring position	0.70	0.01

Figure 4.8 Bland and Altman plot across subjects' 1st and 2nd scoring

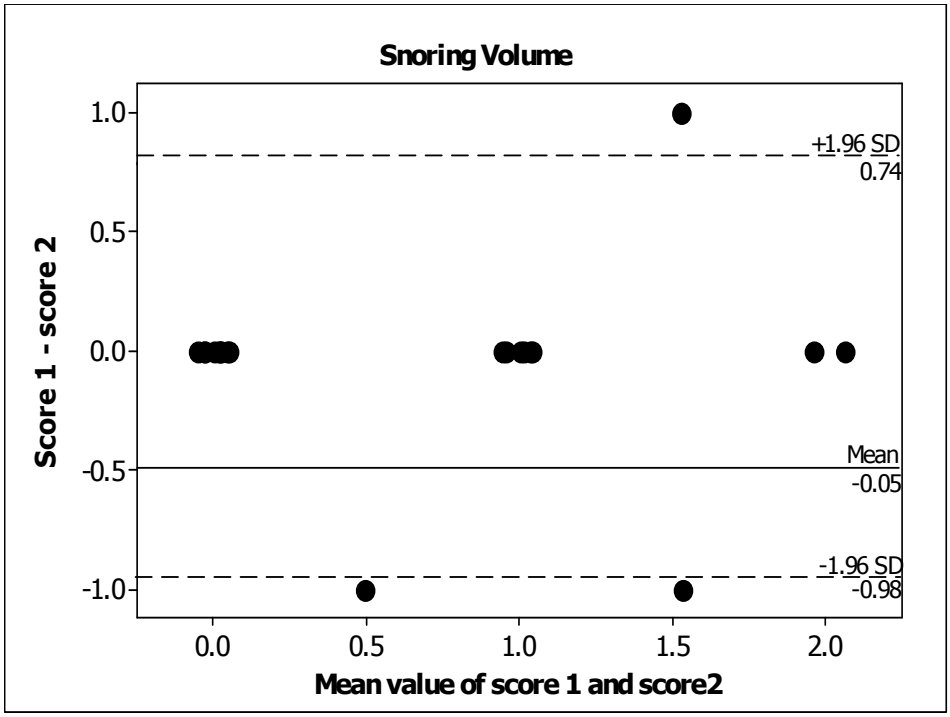
a) Snoring



b) Breathing pauses



c) Snoring volume



d) Snoring position

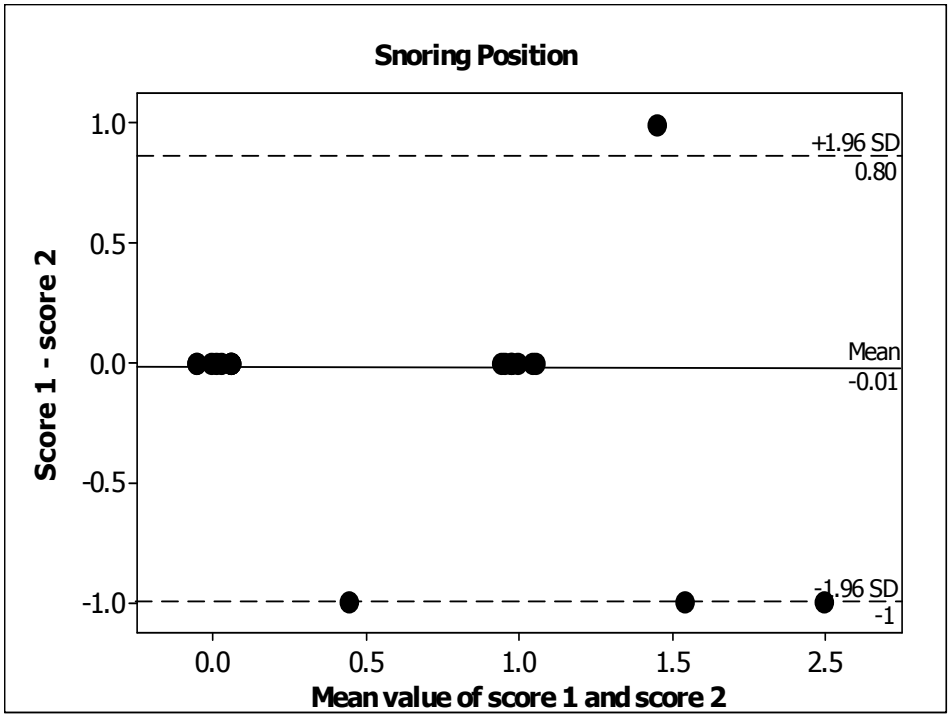
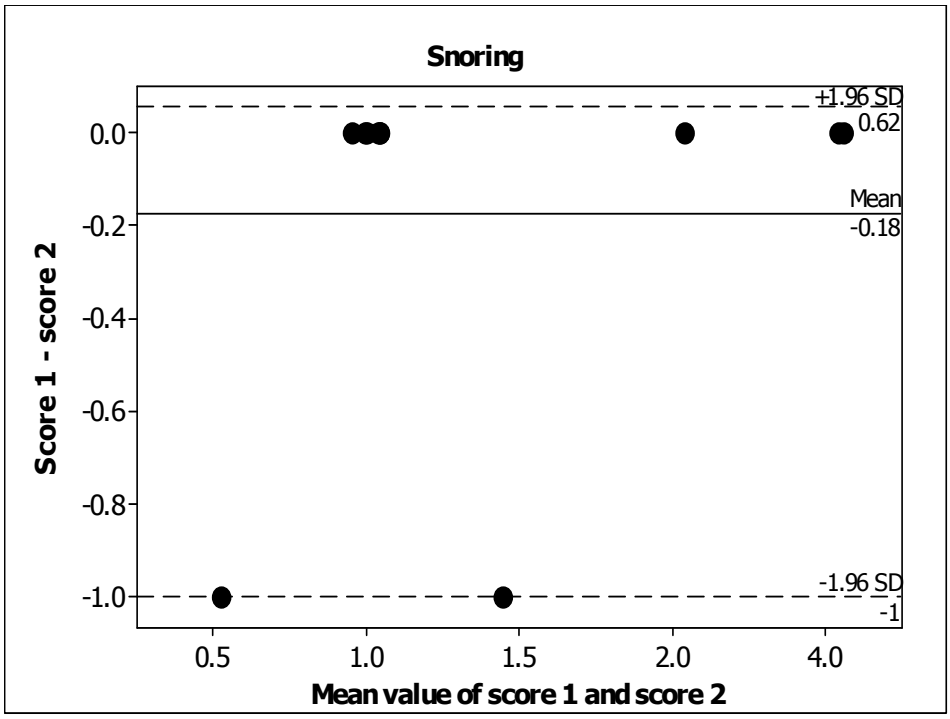
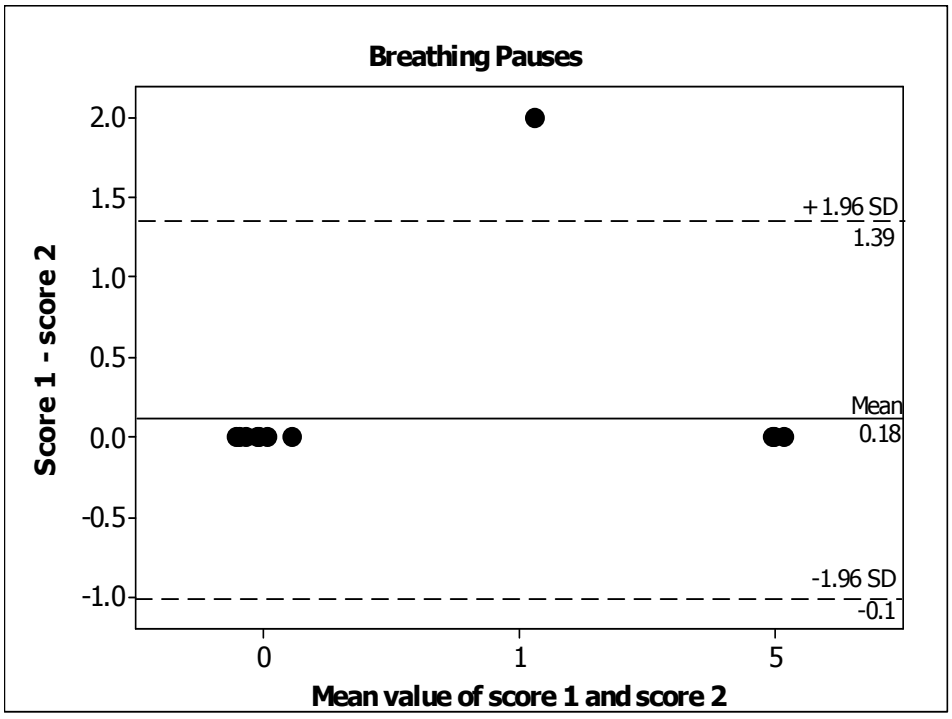


Figure 4.9 Bland and Altman plot across partners' 1st and 2nd scoring

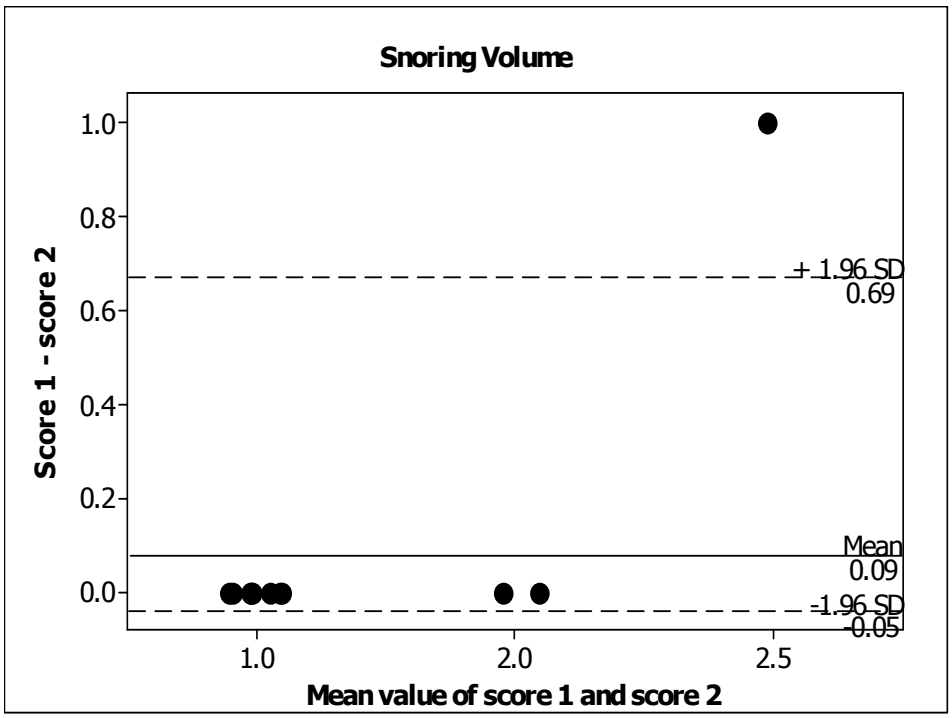
a) Snoring



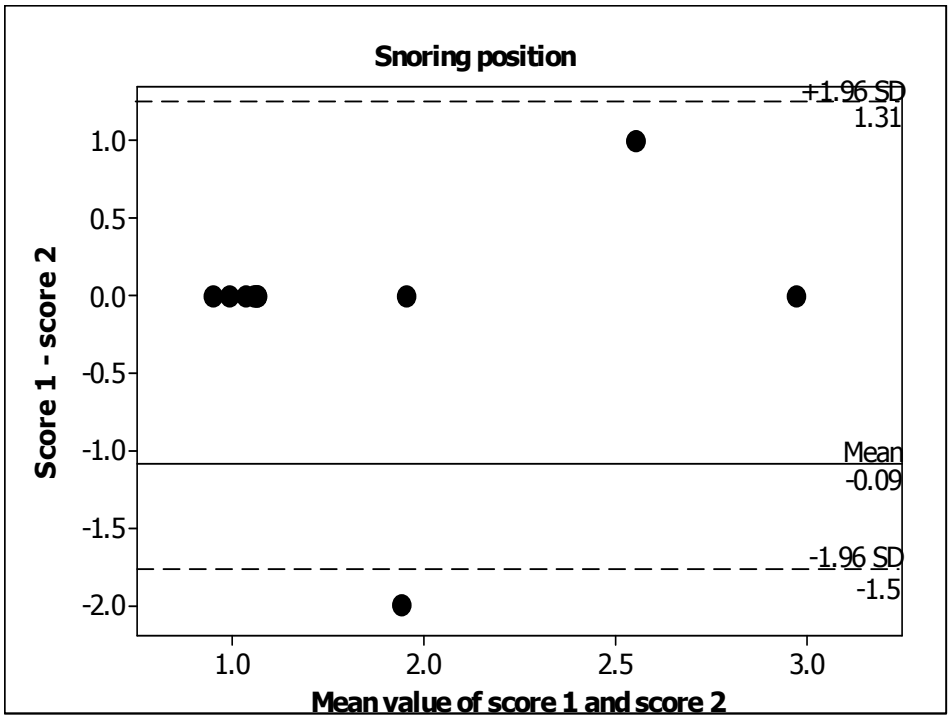
b) Breathing pauses



c) Snoring volume



d) Snoring position



Additi

onally, Cohen's kappa analysis was performed to assess agreement between two answers. The concordance between the answers at a 30-day interval was excellent for the question on frequency of women's snoring (Cohen kappa>0.88, p<0.001). Kappa statistics cannot be computed for the remaining answers due to the limitation of this form of analysis (it requires a symmetric 2-way table in which the values of the first variable match the values of the second variable).

4.4.1 Epworth sleepiness scale (ESS)

The Epworth sleepiness scale is a simple, self administered questionnaire developed by Johns (1991) that evaluates subjective sleepiness. The subject is asked to rate their likelihood of falling asleep in eight everyday situations over the previous month on a scale of 0-3 (0 = no chance of dozing, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing). The Epworth score is the sum of 8 item scores and ranges from 0 to 24. Higher Epworth sleepiness scale scores indicate greater daytime sleepiness.

The Epworth sleepiness scale is widely used in studies of sleep-disordered breathing as a means of quantifying changes in habitual subjective sleep propensity after either an intervention or change within the condition (Engleman et al 2002b, Faccenda et al 2001, Pien et al 2005). Its reliability and validity were examined in different study groups (students, patients and healthy individuals). It has been shown that it has a good test–retest reliability (r=0.82) when applying Epworth sleepiness scale to healthy medical students without any sleep disorders at five months apart and internal consistency (Cronbach alpha=0.74–0.88) (Johns 1991, 1992, 1994). Factor analysis indicated that the

Epworth sleepiness scale has only one factor for healthy medical students and for patients with a variety of sleep disorders (Johns 1992, 1994).

The Epworth sleepiness scale has been validated with the Multiple Sleep Latency Test (MSLT) in patient sample sizes of 27 (Johns 1991), 44 (Johns 1994) and 60 (Chervin et al 1997). It demonstrated a minor but significant correlation with MSLT. Some studies which have compared subjects before and after treatment (Engleman et al 2002b, Faccenda 2001), or at the beginning and at the end of pregnancy also provide some discriminant validity for Epworth sleepiness scale (Pien et al 2005). The Epworth sleepiness scale has a high sensitivity and high specificity with a cut-off score of >10 for an abnormal level of daytime sleepiness (Johns 2000). An example of this scale is shown in appendix C under the title of daytime events in the last month.

●Reproducibility of Epworth sleepiness scale in this thesis

Studies performed in young subjects in the general community, including snorers and non-snorers, demonstrated that there is not a significant gender effect on Epworth sleepiness scale scores. Johns and Hocking (1997) reported that there was no difference between men's and women's Epworth sleepiness scale scores in 331 Australian workers aged 22–59 years (267 men and 64 women). Likewise, a study based in the UK found that Epworth sleepiness scale scores were similar in both female and male control subjects with normal sleep wake habits (ESS: male 5±3, female 4±3) (Parkes et al 1998). Pien et al noted that Epworth sleepiness scale is able to identify increased daytime sleepiness during pregnancy in the same pregnant women (Pien et al 2005). Although these findings suggest that there is not a significant gender effect on Epworth sleepiness scale scores and that Epworth sleepiness scale can identify changes in daytime sleepiness

during pregnancy (Pien et al 2005), in order to ensure that our results were reliable we examined the reliability of ESS in our study group of 20 women.

Test-retest reliability was measured using correlation coefficients (Spearman) and internal consistency measured using Cronbach's ∝, which is a measure of how well items in a scale correlate with one another. Test retest reliability is 0.95 for women's Epworth sleepiness scale and 0.90 for partner's Epworth sleepiness scale (both p=0.01). These findings show that both Epworth sleepiness scales which were used in our studies are highly reliable over time.

Internal consistency was 0.70 for women's Epworth sleepiness scale and 0.71 for partner's Epworth sleepiness scale. These values are within the expected range for a scale to be appropriate for use in comparison of means when groups are considered.

4.4.2 Refreshment five-point Likert scale

The question 'How refreshed do you feel on wakening in the morning regardless of sleep duration?' was rated on a five-point Likert scale from 1 (very unrefreshed) to 5 (fully refreshed). This question was asked to pregnant women both prior to and during their pregnancies.

This question is widely used in sleep units to evaluate individuals for possible sleep-disordered breathing. A similar form (or the Visual Analog Scale) for refreshment, snoring and daytime sleepiness has been used by other researchers successfully (Streiner and Norman 1995, Zielinski et al 1999, Guilleminault et al 2000, Baldwin et al 2004). It

has been shown that this question has significant correlations with excessive daytime sleepiness (Baldwin et al 2004) and snoring (Zielinski et al 1999).

●Validation and reliability of refreshment five-point Likert scale in this thesis Test-retest reliability of the refreshment five-point Likert scale over 30 days time period was 0.80 ($p<0.01$). For construct validity, the Refreshment five-point Likert scale was compared with the Epworth sleepiness scale, using Spearman's correlation coefficient. There was a significant correlation between these scales ($r=-0.67$, $p<0.01$). These results show that this scale is very reliable and adequately valid.

4.5 Summary

In this chapter the recruitment of subjects has been explained, and acoustic reflection technique, and other techniques and questionnaires which were used in these studies have been introduced.

The following chapters include the studies done for this thesis. Chapter five presents a cross-sectional study which investigates the hypotheses that: (1) pregnancy results in UA narrowing; (2) pre-eclampsia is associated with more marked UA narrowing than occurs in normal pregnancy. The second study, which will appear in chapter six, includes a larger cross-sectional study which compares UA size in pregnant and non-pregnant women, and also a longitudinal study which compares UA size before and after pregnancy. The third study, in chapter seven, is a questionnaire-based study. It examines sleep complaints between three groups of women: pregnant, non-pregnant and pre-eclamptic. The fourth study in chapter eight is an uncompleted study which aimed to examine the hypotheses that: (1) upper airway narrowing during sleep occurs more

severely in pre-eclamptic women; (2) overnight diastolic blood pressure in these women can be significantly decreased by 5 mmHg with nasal CPAP when compared to usual therapy. The last chapter of this thesis, chapter nine, summarizes the results and states some possibilities for future work.

CHAPTER 5
THE UPPER AIRWAY IN PREGNANCY AND PRE-ECLAMPSIA

5.1 Introduction

In this cross-sectional study we have investigated the hypotheses that: (1) pregnancy results in UA narrowing; and (2) pre-eclampsia is associated with more marked UA narrowing than occurs in normal pregnancy.

5.2 Methods

5.2.1 Sample size and power

In our previous studies we found a clinically relevant difference of 0.2 cm^2 in OPJ area between patients with OSAHS and normal subjects. We would expect the differences of interest to be smaller in this study. The required sample is 50 pregnant and 50 non-pregnant women to obtain 94% power at the 5% level of detecting a significant difference of 0.1 cm^2 in UA cross-sectional area between pregnant and non-pregnant women. However, this power could be lower than 94% in this study because we used 3-way comparison with 50 pregnant, 50 non-pregnant women and 37 pre-eclamptic women.

5.2.2 Subjects

- **Healthy pregnant women:** To recruit 50 pregnant women, 57 consecutive women in the third trimester of singleton pregnancies were approached at a day assessment unit and antenatal ward and invited to participate in the study and fifty-four agreed. Four were excluded because of inconsistent breathing (n=3) during UA measurements or having severe asthma (n=1). The rest were healthy and met the criteria listed in chapter 4.

● **Pre-eclamptic women:** Pre-eclampsia was defined as the presence of new hypertension (blood pressure > 140/90 or > +30/+15 from booking blood pressure) with proteinuria (> 0.3 g/24 hours) as explained in chapter 4. Forty-seven consecutive patients with pre-eclampsia who attended a high risk clinic or were admitted to the day assessment unit and the antenatal ward in the Simpson Memorial Maternity Pavilion in the Old Royal infirmary were invited to participate in the study. Forty-six agreed but nine were excluded due to pre-existing essential hypertension (n=2), diabetes mellitus (n=2), or having twins (n=2), or inconsistent breathing (n=3) during UA measurements.

● **Healthy non-pregnant women:** Fifty-five healthy non-pregnant women responded. Fifty-two, agreed to be control subjects and all were naive to the purpose of the study. Two were subsequently excluded due to inconsistent breathing during UA measurements.

All subjects gave written informed consent to the study, which had the approval of the local ethical advisory committee.

5.2.3 Protocol

5.2.3.1 Questionnaires

All subjects completed our standard sleep-wake questionnaire, which was mentioned in chapter 4.

5.2.3.2 Measurements

●All had neck, waist and hip circumferences, height, weight, and blood pressure measured.

●UA caliber was measured in each subject using acoustic reflection.

5.2.4 Statistics

Unpaired t-test or one-way ANOVA were used to compare continuous variables with normal distribution, and the Chi-square test was used to compare categoric variables. One-way ANOVA was performed to analyse UA size measurements among three groups; pregnant, pre-eclamptic and non-pregnant women. When ANOVA showed significant differences, differences between groups were determined by the Student-Neuman-Keuls multiple comparison test. An unpaired t-test was used to compare airway calibre measures and blood pressure between snorers and non-snorers. The statistical significance of snoring and breathing pauses among groups was assessed using Chi-square test with Bonferroni correction for multiple comparisons when appropriate. In order to detect significant differences in snoring and breathing pauses a Bonferroni adjusted p value (p value*3) was used.

Results are presented with mean and standard deviation (±SD) or standard error of the mean (±SEM) as indicated. P values of 0.05 or less were taken as significant.

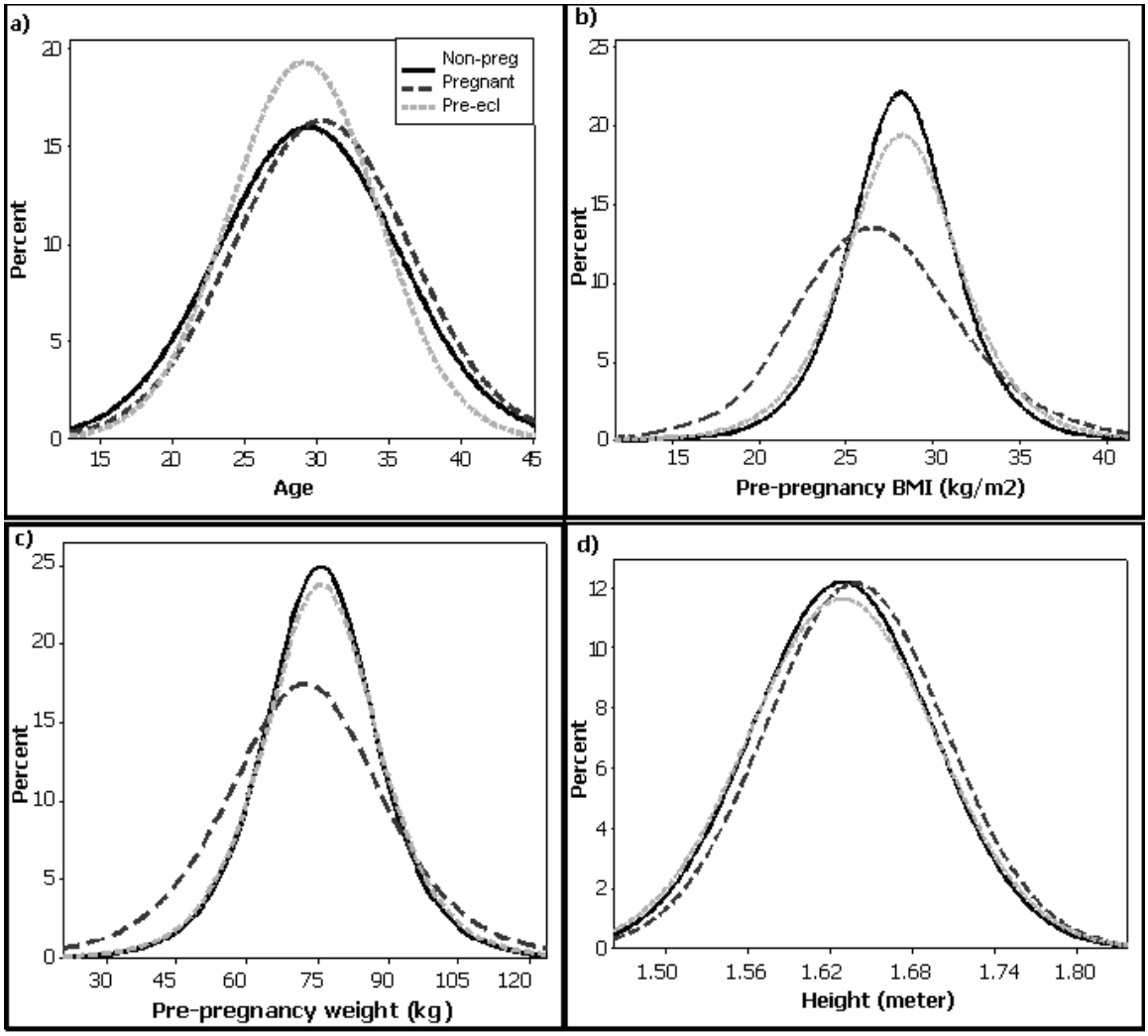
5.3 Results

5.3.1 Subject Characteristics

In this study, I made comparisons between 50 non-pregnant women, 50 pregnant, and 37 pre-eclamptic women for mean age (29 (±SD 6), 30 (6) and 29 (5) yrs respectively), mean pre-pregnancy BMI (24 (3), 24 (6) and 24 (4) kg/m2 respectively), mean pre-

pregnancy weight (64 (10) and 64 (16), 65 (12) kg respectively) and mean height (1.63 (0.1), 1.64 (0.1) and 1.63 (0.1) meter respectively). Also healthy pregnant and pre-eclamptic women were compared for mean duration of pregnancy (36 (3.5) and 36 (3.3) weeks respectively). These three groups were similar in mean age, pre-pregnancy BMI, weight and height (Figure 5.1), and healthy pregnant women and pre-eclamtic women have similar mean duration of pregnancy.

Figure 5.1 Comparisons of a) mean age b) mean pre-pregnancy BMIs c) mean pre-pregnancy weights and d) mean heights between non-pregnant women, pregnant, and pre-eclamptic women



There was no difference between the pregnant women and the control subjects in measured neck circumference on the day that UA dimensions were measured between the pregnant women and the control subjects. However, the women with pre-eclampsia had significantly larger neck circumferences than the normal pregnant and non-pregnant women (35 (±SD 2), 34 (2) and 33 (2) respectively, both $p<0.05$).

Snoring and breathing pauses: Snoring status was reported as unknown by both the women and their partners by thirteen percent of the non-pregnant, 11% of the pregnant women, 13% of women with pre-eclampsia. Of those who reported snoring status, 15% of control women, 28% of pregnant women, and 48% of the patients with pre-eclampsia and their partners reported that they snored on at least three nights per week at the time of study ($p<0.02$) (Table 5.1). When snoring percentages were compared between pregnant, non-pregnant, and pre-eclamptic women individually, with Chi-square tests followed by Bonferroni correction, only the percentage of occasional snoring between pregnant and pre-eclamptic women, and non-pregnant and pre-eclamptic women were significant. However, our major interest was the significance of habitual snoring between non-pregnant and pre-eclamptic women, which only shows a trend towards significance ($p=0.12$) if the conservative Bonferroni correction is applied.

Neither the women nor their partners knew whether the women had breathing pauses in twenty-seven percent of non-pregnant, 24% of pregnant and 48% of pre-eclamptic women. Six percent of non-pregnant, 9% of pregnant and 27% of pre-eclamptic women were reported to have breathing pauses ($P>0.13$) (Table 5.1).

Table 5.1 Percentage of snoring and breathing pauses reported by both the women and partners

	Non-preg n=50	**Preg n=50**	**Pre-ecl n=37**	**Corrected p value Non pregnant vs Pregnant**	**Corrected p value Pregnant vs Pre-eclampsia**	**Corrected p value Non-preg vs Pre-eclampsia**
Habitual snoring in last month	15%	28%	48%	0.57	0.24	0.12
Snoring in last month including occasional snoring	20%	52%	85%	0.3	0.02	<0.003
Breathing Pauses in last month	6%	9%	27%	2	0.6	0.18
Habitual snoring pre-preg period	15%	5%	11%		0.93	
Snoring in pre-preg period including occasional snoring	20%	19%	33%		0.48	
Breathing Pauses in pre-preg period	6%	6%	7%		0.26	

5.3.2 Upper Airway Dimensions

Analysis of variance showed significant differences in many UA dimensions between groups (Table 5.2). Subsequent comparison tests showed:

Table 5.2 Airway calibre measures with results of the student-neuman-keuls multiple comparison tests for measurements where there was a significant difference in analysis of variance

	Nonpregnant (n = 50)	Pregnant (n = 50)	Pre-eclampsia (n = 37)	p value Non pregnant vs Pregnant	p value Pregnant vs Pre-eclampsia	p value Nonpregnant versus Pre-eclampsia	p value for ANOVA
UA: seated							
OPJ, cm^2	1.1 (0.1)	1.3 (0.1)	0.9 (0.1)	0.02	0.01	0.01	<0.001
CSA.mean, cm^2	1.6 (0.1)	1.8 (0.1)	1.4 (0.1)	0.02	0.01	0.08	0.001
Vp, cm^3	15 (1)	19 (1)	13 (1)	0.01	0.01	0.23	0.001
UA: supine							
OPJ, cm^2	1 (0.1)	0.9 (0.1)	0.8 (0.1)	0.31	0.058	0.01	0.02
CSA.mean, cm^2	1.4 (0.04)	1.3 (0.1)	1.2 (0.1)	0.16	0.11	0.01	0.01
Vp, cm^3	14 (0.7)	13 (0.8)	12 (0.7)	0.36	0.15	<0.05	0.07
UA: Lateral							
OPJ, cm^2	1.1 (0.04)	1.0 (0.1)	1.0 (0.1)	0.8	0.9	0.8	0.8
CSA.mean, cm^2	1.5 (0.04)	1.5 (0.1)	1.4 (0.1)	0.76	0.75	0.75	0.8
Vp, cm^3	14 (0.6)	15 (1.1)	14 (0.8)	0.68	0.50	0.50	0.5
Change from the seated to supine posture							
OPJ (%)	4 (6)	27 (3)	7 (5)	0.01	0.01	0.6	0.001
Ap mean (%)	5 (4)	24 (3)	8 (4)	0.01	0.01	0.6	0.001
Vp (%)	-2 (6)	22 (5)	6 (6)	0.01	0.056	0.6	0.01

Abbreviations: ANOVA = analysis of variance; CSA.mean = mean pharyngeal cross sectional area; OPJ = oropharyngeal junction; Vp = pharyngeal volume. Values presented are means ± SEM.

Seated: The pregnant women had wider UAs compared with the non-pregnant women (Table 5.2) as assessed by OPJ area, mean pharyngeal area and mean pharyngeal volume. Patients with pre-eclampsia had narrower pharynxes at the OPJ compared with both non-pregnant and pregnant women (Table 5.2) and smaller mean pharyngeal areas and volumes compared with the pregnant women.

Supine: There was no difference in UA calibre between pregnant and non-pregnant women in the supine posture. Women with pre-eclampsia had narrower OPJs and mean pharyngeal areas than the non-pregnant women. The OPJ also tended ($p = 0.06$) to be narrower in the women with pre-eclampsia than in the pregnant women (Table 5.2).

Lateral: There were no differences between groups in airway size when lying in the left lateral position.

Percentage upper airway narrowing from the seated to supine posture: The UAs of pregnant women narrowed more markedly when lying down than did those of either the normal women or women with pre-eclampsia (Table 5.2).

Relationship of snoring to airway size and blood pressure: In non-pregnant women there were no significant differences between habitual snorers and non-snorers in UA sizes. Across all pregnant women, seated pharyngeal volume (habitual snorers 14 ±SEM1.02, non-snorers 19±1.4, cm^3 $p<0.03$) and supine mean pharyngeal areas (1.2±0.05, 1.3±0.07, cm^2 $p<0.05$) were narrower in snorers than non-snorers (Table 5.3).

There were no significant differences between snorers and non-snorers in systemic blood pressure ($p>0.7$).

Table 5.3 Comparisons of airway calibre measures between snorers and non-snorers across non-pregnant and pregnant women (healthy pregnant and pre-eclamptic women), using unpaired t-test

	Non-pregnant women			**Pregnant women**		
	Snorers	**Non-snorers**	**P**	**Snorers**	**Non-snorers**	**P**
UA: seated						
OPJ, cm^2	1(0.1)	1(0.1)	0.2	1.1(0.05)	1.2(0.07)	0.09
CSA.mean, cm^2	1.5(0.2)	1.6(0.1)	0.4	1.5(0.1)	1.7(0.1)	0.08
Vp, cm^3	13.9(2.2)	15.1(0.8)	0.5	14(1.02)	19(1.4)	<0.03
UA: supine						
OPJ, cm^2	0.9(0.1)	1(0.1)	0.2	0.8(0.05)	0.9(0.05)	0.8
CSA.mean, cm^2	1.3(0.1)	1.4(0.04)	0.4	1.2(0.05)	1.3(0.07)	<0.05
Vp, cm^3	13.4(1.9)	14.4(0.8)	0.8	12.5(0.9)	13.4(0.8)	0.5
UA: Lateral						
OPJ, cm^2	1(0.1)	1.2(0.1)	0.6	1.06(0.08)	1.05(0.06)	0.9
CSA.mean, cm^2	1.3(0.1)	1.5(0.04)	0.1	1.4(0.1)	1.5(0.08)	0.5
Vp, cm^3	12.4(1.6)	15.4(0.8)	0.1	15.2(1.6)	15.9(1.01)	0.7

Values presented are means ± SEM.

5.4 Discussion

5.4.1 The Upper Airway in Pre-eclampsia

The patients with pre-eclampsia had significantly narrower UAs when seated than the non-pregnant women or those with normal pregnancies. When supine, patients with

pre-eclampsia had significantly narrower UAs than the non-pregnant women, with a trend toward also having narrower airways than the pregnant women ($p = 0.058$). These results are in keeping with our hypothesis that UA narrowing is greater in patients with pre-eclampsia than healthy pregnant and non-pregnant women. UA narrowing can be greater during sleep due to loss of muscle tone. In fact, in the current study pre-eclamptic women snored more than healthy pregnant women and non-pregnant women due almost certainly to increased UA resistance. These findings may suggest an association between sleep-disordered breathing and pre-eclampsia, but they do not prove whether this is a causative factor for pre-eclampsia.

These data were probably the result of the difference in soft tissue deposition in the neck, as the women with pre-eclampsia had larger neck circumferences than both the non-pregnant women and those with normal pregnancies. This is most likely due to tissue oedema (Pilkington et al 1995, Longo et al 2003), as most of the women with pre-eclampsia had significant oedema. Yet the development of snoring in pre-eclampsia has been reported to precede the clinical manifestations of pre-eclampsia. However, differential fat deposition in the UA could be a factor, as pre-eclamptic women had larger neck circumferences than the normal pregnant and non-pregnant women. Clarification of these questions will require the use of different imaging techniques, and determination of whether this difference pre-existed or occurred during pregnancy will require prospective study. The displacement of the diaphragm by the enlargement of abdominal mass loading might also influence UA size due to the reduction in FRC which is characteristic of pregnancy. Furthermore, pre-eclamptic women may have a larger abdominal loading than healthy pregnant women. For example the incidence of pre-eclampsia is increased in multiple pregnancies – although these were excluded from

our study – and women with high baseline BMI (Duckitt and Harrington 2005). Thus increased abdominal loading due to multiple pregnancies or abdominal fat can lead to more serious UA narrowing in pre-eclamptic women, but this is not the case in this study because multiple pregnancies were excluded and pre-pregnancy BMI was similar between pregnant and pre-eclamptic women.

The narrower UA observed in women with pre-eclampsia is compatible with the observation of increased UAs airflow limitation during sleep in pre-eclampsia (Edwards et al 2000b, Connolly et al 2001). These episodes may be associated with arousals and with surges in blood pressure (Edwards et al 2000b, Edwards et al 2001) in an already compromised circulatory system. CPAP can reduce mean 24-hour blood pressure in patients with the obstructive sleep apnoea/hypopnoea syndrome (Faccenda et al 2001, Pepperell et al 2002) where UA narrowing during sleep causes blood pressure surges. Preliminary reports indicate that in patients with pre-eclampsia, CPAP may improve both sleep and blood pressure control (Edwards et al 2000b, Connolly et al 2001). However, the role of CPAP in the management of pre-eclampsia requires further study.

5.4.2 Effects of Pregnancy on the Upper Airway

This study found that the UA in the third trimester of pregnancy was wider in the seated position but of similar calibre in the supine posture when compared with non-pregnant women.

These results were not expected as the prevalence of snoring is increased in pregnant women (Loube et al 1996, Franklin et al 2000, Lueng et al 2005) and thus the airway

would be expected to be narrower during pregnancy. Factors which may have contributed to this finding are:

1. Although age and pre-existing BMI were similar in the pregnant and non-pregnant women, they came from different subsets of the Edinburgh population although both groups were 98% white. The identification of health inequalities will always occur when working with collective groups (social class, race, ethnicity, e.g.). Social class bias may possibly occur between the pregnant and non-pregnant women. The non-pregnant women were mostly hospital staff who had a certain income and educational level, but the pregnant women were a mixture. Some of them were very young single mother while others were well educated and more mature. In this aspect it was difficult to control social factors. For example, there can be an association between social class and fitness. Also subjects did not have an ENT examination to distinguish women who have UA abnormalities. Subjects with abnormal UA anatomy would already have small UAs compared to women with similar BMI etc. Thus the unexpected results of our study could be explained by various reasons which we could not control.

2. A longitudinal study in the same women comparing UA dimensions before and during pregnancy would a better method of identifying the effect of pregnancy on UA, by removing the between subject variability inherent in cross-sectional studies. However, I managed to recruit only 16 of these 50 pregnant women for restudy after their pregnancy. This was not a sufficient number to compare UA size before and after pregnancy. Therefore this comparison was not reported in this study. This is detailed in chapter 6.

3. Many comparisons were performed in the course of the statistical analysis. Fifty-six comparisons (Tables 5.3 and 5.4) were done on airway size and thus 2.8 (56/20) of these would be expected to show significant difference by chance at the p=0.05 level. Thus our positive but unexpected finding of increased UA dimensions during pregnancy might be a chance finding on this basis.

4. Sleep leads to a progressive loss of UA muscle tone and increase of UA resistance (Remmers et al 1978, Tsushima et al 1996). However, studies reported that the activity of pharyngeal dilator muscles is increased during wakefulness in individuals with sleep-disordered breathing (Mezzanotte et al. 1992, Fogel et al. 2003c, Fogel et al 2005). Thus even if pregnant women have UA narrowing, while they are awake they may overcome the abnormal UA narrowing.

5. Studies show that the collapsibility of the UA occurs in the supine position rather than seated (Martin et al 1995 and 1997), due to gravity and tissue pressure (Fouke and Strohl 1987, Deegan et al 1995). In this study UA measurements were not significantly different between pregnant and non-pregnant women in the supine position.

The pregnant women had a much larger decrease in airway calibre upon lying down. A similar supine UAs calibre but larger percentage narrowing upon lying down has also been found in men compared with non-pregnant women (Martin et al 1997), and men have a higher prevalence of snoring than women (Young et al 1993, Ohayon et al 1997). It is thus possible that the degree of UA narrowing on lying down is related to snoring and a better predictor of snoring than any absolute measure during wakefulness. This could perhaps be related to the UA dilating muscles managing by increased activity to

preserve airway calibre when seated but being unable to increase their activity on lying down. Thus when sleep reduces the activity of these muscles, UA calibre is reduced more in those with high dilating tone in wakefulness and snoring or airflow limitation occurs.

As the neck diameters were not different with pregnancy, it seems unlikely that there was differential local mass loading directly on the UA. Earlier studies demonstrated that FRC is decreased by 15–25% in pregnancy in seated and supine positions (Gee et al 1967, Craig and Toole 1975, Holdcroft et al 1977) due to increased abdominal mass raising the diaphragm. In turn, the decreased FRC and tracheal shortening can produce UA narrowing (Hoffstein et al 1984, Burger et al 1992), and this seems the most likely explanation for the reduction in airway calibre upon lying down in pregnant women in the current study. However, pregnant women did not have smaller UA in both seated and supine position in comparison to non-pregnant women. Some factors as mentioned above may affect our results. The previous studies compared FRC within groups before and after pregnancy (Gee et al 1967, Craig and Toole 1975, Holdcroft et al 1977). This may provide better control of some confounding factors such as social class, anatomical predisposition to UA narrowing etc. Thus a further study is needed to compare UA size within groups before and after pregnancy or during and after pregnancy.

The limitations of this study include its cross-sectional design and potential selection biases between the groups of subjects. A cross-sectional study cannot prove cause and effect, but merely suggest causation if other known influences are excluded. Factors that may affect UA size include gender (Brown et al 1986, Brooks and Strohl 1992, Martin et al 1997, Malhotra et al 2002), age (Martin et al 1997, Fogel et al 2005), obesity (Martin et

al 1997, Peppard et al 2000a, Fogel et al 2003a), familial factors (Mathur and Douglas 1995b), and sleep state (Trinder et al 1997, O'Connor et al 2000, Thurnheer et al 2001). However, in this study these factors were controlled.

Another limitation is the fact that the acoustic reflection technique can only measure UA size via the oral route and thus misses the retropalatal airway, which may be the site of the critical airway narrowing during sleep (Schwab et al 1993a, Schwab et al 1995, Isono et al 1997, Isono et al 2003, Schwab et al 2003). Nevertheless, the technique has been previously shown to be a useful tool to discriminate changes in UA size with sleep apnoea (Rivlin et al 1984, Bradley et al 1986), snoring (Bradley et al 1986), obesity (Martin et al 1997), age (Martin et al 1997), and posture (Jan et al 1994, Martin et al 1997) Furthermore, the measurements can only be performed in awake subjects; thus, care must be taken in extrapolating the results to differences, which may exist during sleep.

In conclusion, this study shows that there is airway narrowing in patients with pre-eclampsia, which may explain why such patients have increases in UAs resistance with associated consequent rises in blood pressure during sleep.

CHAPTER 6
SLEEP-DISORDERED BREATHING AND UPPER AIRWAY SIZE IN PREGNANCY AND POSTPARTUM

6.1 Introduction

In the previous chapter, pre-eclamptic women were found to have UA narrowing compared to non-pregnant or normal pregnant women. The effect of pregnancy on the UA was unclear and to some extent counter-intuitive, with pregnant women having larger airways when seated compared to non-pregnant women, but with greater narrowing on lying down and a non-significant trend to have narrower airways than non-pregnant women when supine.

Because that study was relatively small with statistical power further reduced by 3-way comparisons. I performed a larger and more powerful study to compare UA size in pregnant and non-pregnant women. I also incorporated a within-subject prospective study to clarify possible changes in UA calibre following pregnancy.

6.2 Methods

Sample size and power

In this study, we performed a new power calculation using data from the earlier study (Martin et al 1995). A sample size of 100 pregnant and 100 non-pregnant women gives 88% power at the 5% level to detect a 13% difference in UA cross-sectional area at the OPJ (Martin et al 1995).

6.2.1 Subjects

●Healthy pregnant women: One-hundred and thirty-eight women in the third trimester of their pregnancies attending a day assessment unit or admitted to the antenatal ward were consecutively considered for participation in this study as explained in chapter 4. One-hundred of these took part in the study, while thirty-eight were excluded since they had twins (n=3), essential or gestational hypertension (n=7) or pre-eclampsia (n=3), diabetes mellitus (n=8), severe asthma (n=2) or cystic fibrosis (n=1), or were pregnant less than 28 weeks (n=3), or were unable to stay for UA measurement, having filled out the questionnaire (n=5), or inconsistent breathing (n=6).

●Healthy non-pregnant women: One-hundred and twenty non-pregnant women, mainly hospital staff, were randomly selected from advertisement respondents as explained in chapter 4. One-hundred and twelve of them agreed to take part in the study. Twelve of them were excluded due to being morbidly obese (BMI>35kg/m2; n=2), older than 45 (n=4), suffering from hypertension (n=2) or a respiratory infection (n=1), or inconsistent breathing (n=3) during UA measurements. None of the recruited pregnant or the non-pregnant women participated in our previous study (Chapter 5, Izci et al 2003).

●Women in the post-partum study: All the pregnant women studied, including the subjects from the first study, were informed about the possibility of the follow-up study when initially studied. Their expected delivery date was sought from both the women and their case notes. At least three months after their delivery, a letter (Appendix E) together with the standard sleep-wake questionnaires (both subject and partner, Appendix A and D), which had a few details changed to fit with their post

partum status, were sent to invite them to participate in the follow-up study. They were then contacted by phone, and if they agreed to be restudied, we arranged a suitable time (generally when they were visiting the hospital for their routine screening) for the UA measurement, and provided more information, if they requested it. The possibility of a new pregnancy was specifically asked about, and if they were known to be pregnant they would have been excluded; however, none were.

Fifty agreed to be re-studied (16 from first study (Chapter 5, Izci et al 2003) and 34 from this study). The rest were not able to attend the follow-up study due to the demands on new mothers, travel problems (n= 30), moving house (n= 5), taking care of other children (n= 27), recommencing work (n= 23), could not reach (4) and reason not given (11).

All gave written, informed consent to the studies which were approved by the Ethical Advisory Committee.

6.2.2 Protocol

6.2.2.1 Questionnaires

All subjects and their partners completed the standard sleep-wake questionnaires (chapter 4). Criteria for snoring and breathing pauses were explained in chapter 4.

To assess possible reporting bias due to 45/100 non-pregnant women having no partner when originally approached, a second questionnaire was sent to a current partner or an occasional room-sharer of these women, asking for information on the women's snoring and breathing pauses around 3 months later. The 20 returned questionnaires showed no significant difference between the partners' and these women's reports of

snoring (p=0.25) or breathing pauses (p=0.23) when compared to the reports of their current partner or room-sharer.

6.2.2.2 Measurements

●All had height, weight, waist and hip circumferences, neck circumferences, blood pressure and UA calibre measured. These measurements and questionnaires were repeated postpartum.

●Blood pressure was recorded.

●Upper-Airway Measurement: Each subject had UA calibre measured using the acoustic reflection technique which is described in chapter 4 (Marshall et al 1993a, Martin et al 1995, Martin et al 1997). Five measurements were recorded in the seated, supine and left-lateral positions, and all were stored. OPJ, mean pharyngeal area and mean pharyngeal volume from the traces (see fig. 4.3) were measured as previously described in chapter 4 (Marshall et al 1993a, Martin et al 1995, Martin et al 1997).

6.2.3 Statistical Analysis

The statistical significance between the groups was assessed using unpaired t-test and Chi-square test for independent variables and paired t-test and McNemar test were used to analyse variables within groups before and after pregnancy in the same group. Bonferroni correction also was used by adjusting the p-value (p value*3) due to multiple comparisons of snoring and breathing pauses before, during and after pregnancy. An unpaired t-test was used to compare airway calibre measures and blood pressure between snorers and non-snorers, etc. Correlations were performed using the Pearson's coefficient of correlation to show association between blood pressure and UA size. Results are presented as mean with standard deviation (±SD) or standard error of the

mean (±SEM). A p value <0.05 was used to indicate statistical significance. SPSS for Windows was used for analysis.

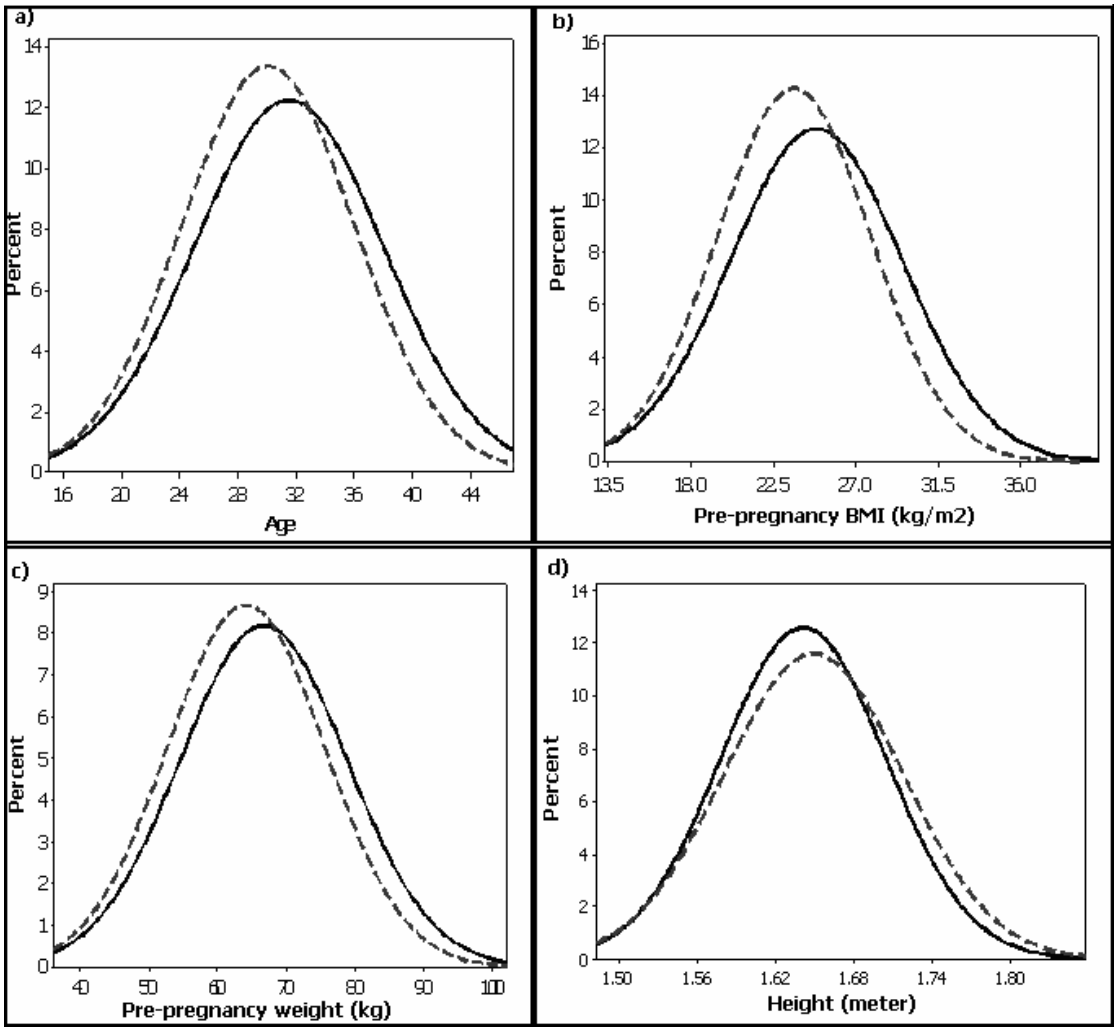
6.3 Results

6.3.1 Subject characteristics

In this study, we compared 100 non-pregnant women and 100 pregnant for mean age (31.5 (±SD 6.5) and 30 (6) yrs respectively), mean pre-pregnancy BMI (24.8 (4.7) and 23.6 (4) kg/m2 respectively), mean pre-pregnancy weight (66.6 (12) and 64 (11.5) kg respectively) and mean height (1.64 (0.1) and 1.65 (0.1) meter respectively). These two groups were similar in mean age, pre-pregnancy BMI, weight and height (Figure 6.1).

Neck circumferences were not different between the pregnant women and the non-pregnant women, on the day UA dimensions measured (33.4 (±SD 2) and 33 (2) cm respectively, p >0.1). The mean duration of gestation of all the pregnant women who were recruited was 36 (3) weeks.

Figure 6.1 Comparisons of a) mean age b) mean pre-pregnancy BMIs c) mean pre-pregnancy weights and d) mean heights between non-pregnant women and pregnant women



The pregnant women, who were restudied postpartum, were compared with those who were not restudied. The groups did not differ in terms of the main demographic characteristics, which include: the mean duration of gestation (those restudied 36±4 vs 36±4 weeks; p=0.25), neck circumferences (33.6±2 vs 33.4±2 cm; p=0.58), height (1.66±0.1 vs 1.65±0.1 m; p=0.38), pregnancy BMI (28±4 vs 27±5 kg/m2; p=0.21), pre-pregnancy BMI (24±4 vs 23±4 kg/m2; p=0.13) and pre-pregnancy weight (66±11 vs 63±11 kg; p=0.11) but were older (those restudied 33±4 vs 28±6 yr; p<0.001). They did

not differ in clinical features: snoring ($p=0.09$), breathing pauses ($p=0.68$) or UA cross sectional areas (all $p>0.07$). Twenty-nine percent women who did not join the follow-up study snored and 45% of women snored of those involved in the follow-up study. Additionally, there were 15% who had breathing pauses amongst those not joining follow-up and 11% amongst those who did join it.

6.3.2 Comparative study

●Differences in UA dimensions between non-pregnant and pregnant women: Pregnant women had significantly smaller UAs at the OPJ when seated and smaller mean pharyngeal areas in the seated, supine and lateral postures compared to the non-pregnant women (Table 6.1). All other UA dimensions in all postures were numerically narrower in pregnancy, but these differences were not statistically significant. There were no differences in the percentage narrowing in the UA on lying supine between pregnant and non-pregnant women.

Table 6.1 Mean (±SEM) of airway calibre measures

	Non-pregnant (n =100)	Pregnant (n =100)	Differences		P value
			Mean	95% CI	
Upper airway: seated					
OPJ, cm^2	1.39 (0.05)	1.27 (0.04)	0.12	0.008 to 0.25	<0.04
CSA.mean, cm^2	1.84 (0.05)	1.70 (0.05)	0.14	0.001 to 0.28	<0.05
Vp, cm^3	20.15 (0.72)	18.66 (0.55)	1.49	-0.30 to 3.28	0.10
Upper airway: supine					
OPJ, cm^2	1.15 (0.04)	1.07 (0.03)	0.08	-0.01 to 0.17	0.09
CSA.mean, cm^2	1.62 (0.04)	1.51 (0.03)	0.11	0.01 to 0.22	<0.03
Vp, cm^3	17.54 (0.54)	16.35 (0.49)	1.19	-0.26 to 2.63	0.10
Upper airway: Lateral					
OPJ, cm^2	1.23 (0.03)	1.17 (0.03)	0.06	-0.03 to 0.15	0.18
CSA.mean, cm^2	1.71 (0.04)	1.58 (0.04)	0.13	0.02 to 0.24	0.02
Vp, cm^3	18.33 (0.52)	17.40 (0.56)	0.93	-0.57 to 2.43	0.22
Δ % from the seated to supine posture					
OPJ (%)	12 (4)	9 (3)	2	-8 to12	0.63
CSA.mean (%)	9 (3)	6 (3)	3	-5 to 11	0.46
Vp (%)	7 (3)	6 (4)	2	-9 to 12	0.78

Abbreviations: SEM = standard error of the mean; OPJ = oropharyngeal junction, CSA.mean = mean pharyngeal cross-sectional area; Vp = pharyngeal volume; CI = confidence intervals.

6.3.3 The prevalence of snoring and breathing pauses

The prevalence of snoring frequency is presented in table 6.2. When "never", "rare" and "occasional" snoring was considered as non-snoring in order to compare snoring status between habitual snorers and non-snorers, seventeen percent of the non-pregnant

women were habitual snorers compared to 41% of the pregnant women ($p<0.001$). Twelve percent of the pregnant women reported that they were habitual snorers prior to becoming pregnant ($p=0.35$ compared to non-pregnant women).

Table 6.2 The percentage of snoring frequency by pregnancy status

	Never/ Rare snoring	**Occasional snoring**	**Habitual snoring**	**Don't know**	**Total**
Non-pregnant women	62%	16%	16%	6%	%100
Pregnant women	38%	19%	39%	4%	%100
Pregnant women before pregnancy	64%	18%	11%	7%	%100
Post-partum women	69%	11%	18%	2%	%100
Postpartum women in pregnancy	22%	19%	59%	—	%100
Postpartum women before pregnancy	68%	16%	10%	6%	%100

Thirty-one percent of pregnant and 22% of non-pregnant women, and their partners, did not know if the women had breathing pauses. Seventy-four percent of the non-pregnant and 54% of the pregnant women never had breathing pauses, 2% non-pregnant and 5% pregnant women occasionally had breathing pauses, while 2% non-pregnant and 10% pregnant women reported that they had breathing pauses frequently or always. Again "never", "rare" and "occasional" answers were taken to mean no breathing pauses. In this situation, 3% of non-pregnant women had been reported to have breathing pauses (often, frequently or always) in comparison to 14% of pregnant

women (p=0.02). Breathing pauses were reported in 19% of snoring pregnant women, as compared with 12% of the non-snoring pregnant women (p=0.46).

Comparing responses between the 3 groups and using the Bonferroni correction throughout, the group studied postpartum, habitual snoring occurred in 11% before pregnancy and 59% in the third trimester (adjusted p<0.003). After delivery, the percentage snoring decreased to 18% (adjusted p<0.003 compared to pregnancy level). Fifteen percent of pregnant women reported breathing pauses in the third trimester of pregnancy while only 5% of them reported breathing pauses postpartum (adjusted p<0.003). None of them reported breathing pauses before pregnancy (adjusted p<0.003 comparison with pregnancy period). Twenty-five percent of snoring women reported that they had breathing pauses compared to 0% of non-snoring women in pregnancy period (p< 0.001).

●Snoring in pregnant, non-pregnant women and women in postpartum period: Pregnant women who snored were heavier (snorers: 68±11, non-snorers: 62±10 kg; p=0.01), had higher BMIs before pregnancy (snorers: 25±5, non-snorers: 23±4 kg/m2; p=0.008) and during pregnancy (weight-snorers: 79±11, non-snorers: 73±13 kg; p=0.04, BMI-snorers: 29±4, non-snorers: 27±4 kg/m2; p=0.03). Snoring pregnant women had a tendency to have larger neck circumferences (snorers: 34±2, non-snorers: 33±2 cm; p=0.052) than non-snorers. Systolic blood pressure was higher in snoring pregnant women (snorers: 120 ±SE 2, non-snorers: 112±2 mmHg; p=0.006) than non- snorers. Also, snoring women in postpartum had larger neck circumferences (snorers: 34±2, non-snorers: 32±2 cm; p=0.008) but BMI, weight and blood pressure did not differ between snorers and non-snorers in postpartum (both p>0.07). Regarding

BMI, weight, blood pressure and neck circumferences in non-pregnant women, there were no significant differences between snorers and non-snorers (all $p \geq 0.76$).

Habitual snoring was not associated with any UA size differences among either pregnancy, postpartum or non-pregnant women (all $p \geq 0.1$) (Table 6.3).

Table 6.3 Mean (±SEM) of airway calibres between snorers and non-snorers in pregnant, non-pregnant and postpartum women

	Pregnant (n =100)		**P**	**Non-pregnant (n =100)**		**P**	**Postpartum (n=50**		**P**
	Snorers n =35	**Non-snorers n =51**		**Snorers n =15**	**Non-snorer n =73**		**Snorers n =8**	**Non-snorer n =36**	
Upper airway: seated									
OPJ, cm^2	1.23(0.06)	1.29(0.06)	0.39	1.40(0.14)	1.36(0.05)	0.76	1.43(0.19)	1.33(0.08)	0.61
CSA.mean, cm^2	1.65(0.05)	1.74(0.08)	0.35	1.71(0.13)	1.85(0.06)	0.32	1.95(0.09)	1.77(0.07)	0.24
Vp, cm^3	18.95(0.87)	18.69(0.83)	0.83	17.88(1.55)	20.03(0.69)	0.21	23.17(1.93)	19.2 (1.23)	0.16
Upper airway: supine									
OPJ, cm^2	1.07(0.05)	1.05(0.04)	0.77	1.03(0.07)	1.15(0.04)	0.24	1.23(0.10)	1.11(0.05)	0.35
CSA.mean, cm^2	1.49(0.06)	1.51(0.04)	0.77	1.49(0.08)	1.62(0.05)	0.23	1.63(0.09)	1.63(0.07)	0.99
Vp, cm^3	16.7(0.82)	15.7(0.66)	0.33	16.23(1.19)	17.55(0.65)	0.39	17.89(0.79)	16.35(1)	0.24
Upper airway: Lateral									
OPJ, cm^2	1.14(0.05)	1.15(0.05)	0.91	1.15(0.09)	1.23(0.04)	0.40	1.24(0.12)	1.24(0.06)	0.99
CSA.mean, cm^2	1.53(0.06)	1.61(0.06)	0.43	1.65(0.10)	1.69(0.05)	0.65	1.71(0.07)	1.77(0.07)	0.65
Vp, cm^3	16.42(0.88)	18.14(0.85)	0.18	17.02(1.13)	18.48(0.65)	0.34	18.44(1.38)	18 (0.99)	0.84
Δ % from the seated to supine posture									
OPJ (%)	7.15(0 4.94)	10.75(5.68)	0.65	8.65(19.09)	12.96(2.76)	0.83	9.70(6.48)	10.89(4.58)	0.91
CSA.mean (%)	7.93(3.37)	5.09(5.83)	0.71	2.95(14.25)	11.23(2.09)	0.58	19.51(5.56)	8.29(3.33)	0.15
Vp (%)	3.63(6.28)	9.95(6.78)	0.52	-4.33(13.33)	8.94(3.22)	0.16	23.81(5.95)	8.98(5.78)	0.1

Abbreviations: SEM = standard error of the mean; OPJ = oropharyngeal junction; CSA.mean = mean pharyngeal cross-sectional area; Vp = pharyngeal volume

6.3.4 Follow up study

When 50 pregnant women were restudied postpartum, they had lower BMI (28 ±SD 4, 25±4 kg/m2; $p<0.001$) and neck circumferences (34±2, 33±2 cm; $p<0.001$).

●Comparison of UA dimensions in postpartum period and third trimester of pregnancy: Women in the third trimester of pregnancy had smaller mean pharyngeal areas compared to the post-partum period in all 3 postures; seated, supine and lateral (Table 6.4). On lying down, the UAs at the OPJ narrowed more during pregnancy than in the postpartum period (Table 6.4).

Table 6.4 Mean (±SEM) of airway calibre measures

	Post-partum (n =50)	Pregnant (n =50)	Differences		P value
			Mean	95% CI	
Upper airway: seated					
OPJ, cm^2	1.32 (0.07)	1.30 (0.05)	0.02	-0.14 to0.17	0.85
CSA.mean, cm^2	1.80 (0.06)	1.62 (0.05)	0.18	0.02 to 0.32	<0.03
Vp, cm^3	20 (0.99)	19 (0.76)	1	-1.50 to 3.36	0.44
Upper airway: supine					
OPJ, cm^2	1.12 (0.04)	1.06 (0.04)	0.06	-0.07 to 0.19	0.36
CSA.mean, cm^2	1.67 (0.05)	1.47 (0.05)	0.20	0.06 to 0.35	0.007
Vp, cm^3	17.09 (0.79)	16.84 (0.71)	0.25	-1.97 to 2.48	0.82
Upper airway: Lateral					
OPJ, cm^2	1.22 (0.05)	1.18 (0.04)	0.057	-0.47 to 0.16	0.28
CSA.mean, cm^2	1.75 (0.05)	1.49 (0.04)	0.26	0.12 to 0.39	0.001
Vp, cm^3	18.09 (0.81)	16.83 (0.56)	1.26	-0.63 to 3.16	0.19
Δ % from the seated to supine posture					
OPJ (%)	10 (4)	23 (4)	-13	-24 to -1	<0.04
CSA.mean (%)	9 (3)	5 (6)	4	-11 to 19	0.61
Vp (%)	9 (5)	2 (8)	6	-15 to 27	0.55

Abbreviations: SEM = standard error of the mean; OPJ = oropharyngeal junction; CSA.mean = mean pharyngeal cross-sectional area; Vp = pharyngeal volume; CI = confidence intervals

●**Blood Pressure in third trimester of pregnancy:** Pregnant women had higher systolic blood pressure than non-pregnant women (115 ±SEM 1 vs 108±2 mmHg; p=0.001). Pregnant women who participated in the follow-up study had higher

systolic blood pressure in pregnancy than postpartum women (116 ±SEM 2 vs 104±2 mmHg; $p<0.001$).

●Relationship between blood pressure and airway size: In the non-pregnant women, there were negative correlations between mean pharyngeal areas in the seated ($r= -0.23$, $p=0.05$) and supine ($r= -0.23$, $p=0.05$) postures with diastolic blood pressure but no correlations between systolic blood pressure and UA sizes. In the pregnant women, there were negative correlations between systolic blood pressure with seated ($r= -0.2$, $p=0.05$), supine ($r= -0.3$, $p=0.01$) and lateral ($r= -0.3$, $p=0.05$) mean pharyngeal areas and lateral OPJ ($r= -0.23$, $p=0.05$). Diastolic blood pressure did not correlate with any UA sizes. In the post-partum women there were no significant correlations.

●Sleepiness and refreshment: Mean Epworth Sleepiness Scale (ESS) scores were higher during pregnancy than reported pre-pregnancy scores (pregnancy: 7 ±SEM 1, pre-pregnancy:4±1; $p<0.001$). Pregnant women also had higher Epworth Sleepiness Scale scores than non-pregnant women (5±1; $p=0.001$). In the follow-up study, women had higher Epworth Sleepiness Scale scores in pregnancy than postpartum (pregnancy: 8±1, postpartum: 6±1; $p=0.008$).

Pregnant women felt more refreshed on waking in the morning before pregnancy than during the third trimester of pregnancy (pre-pregnancy: 3.6±0.1, pregnancy: 2.8±0.1; $p<0.001$). However, there were no significant differences in refreshment, between non-pregnant and pregnant women or between pregnancy and postpartum period ($p\geq 0.14$).

In the pregnancy and postpartum period, snoring was not associated with either Epworth Sleepiness Scale or refreshment score (both $p>0.3$). In non-pregnant women, snorers were not sleepier than non-snorers but they felt less refreshed than non-snorers on waking in the morning (snorers: 2.3 ± 0.2, non-snorers:3.1 ± 0.1; $p<0.001$).

6.4 Discussion

This study shows that the UA is significantly narrower in awake women in the third trimester of pregnancy than in either non-pregnant or post partum women. All nine measures of UA calibre were numerically smaller in the third trimester of pregnancy and four of these differences were significant, including at least one of the measurements in each posture. In the follow-up study, three of the UA dimensions were significantly narrower in third trimester of pregnancy than postpartum. Although the changes were consistent, they were small, with no greater than 15% narrowing between pregnant and non-pregnant women, and between pregnancy and postpartum period. However, the prevalence of habitual snoring, which often accompanied clinically important sleep-disordered breathing, was considerably higher in pregnant women (Pien et al 2005), strongly supporting our observation of UA narrowing in pregnancy.

There are several studies on sleep-disordered breathing in pregnancy, most are based on questionnaires (Loube et al 1996, Franklin et al 2000, Hedman et al 2002) or clinical examinations (Pilkington et al 1995) or focused on pre-eclampsia (Edwards et al 2000b, Connolly et al 2001, Izci et al 2003). In this study, frequent snoring increased up to 59% in the third trimester compared to the pre-pregnancy (12%) and the postpartum period (18%), and breathing pauses were reported in 14 to 15% in the third trimester of

pregnancy. Although the current study confirms previous studies and case reports (Kowall et al 1989, Lefcourt and Rodis 1996, Loube et al 1996, Edwards et al 2000b, Franklin et al 2000, Guilleminault et al 2000), the percentage of snoring is higher in this study than previous studies perhaps because previous studies focus on the results from only the women (Loube et al 1996) or only the partner (Guilleminault et al 2000, Lee et al 2000), whereas we combined both reports.

The objectively narrower UA in pregnancy is compatible with the suggestion of reduced pharyngeal dimensions during pregnancy demonstrated using visual inspection, classified according to the Mallampati score (Pilkington et al 1995). There are many possible causes for this UA narrowing. These include weight gain (Hoffstein et al 1984, Franklin et al 2000, Maasilta et al 2001, Lueng et al 2005) and abdominal mass loading resulting in decreased lung volume and trachea shortening (Hoffstein et al 1984, Burger et al 1992, Schwab et al 1993b). Previous studies (Franklin et al 2000, Maasilta et al 2001, Lueng et al 2005, Pien et al 2005), as well as the present study have found that habitual snorers were significantly heavier than non-snorers before and during pregnancy. This outcome suggests that both baseline pre-pregnancy BMI and gestational weight gain have an important role in the development of sleep-disordered breathing in pregnancy. This finding was supported by Welch et al, who demonstrated that UA cross-sectional area increased with weight loss in normal women (Welch et al 2002), and they and others observed that weight loss lowered the diaphragm and increased FRC (Hoffstein et al 1984, Welch et al 2002). However, Edwards et al (2005) analyzed the relationship between weight lost and improvement in AHI between the antenatal and postnatal studies and revealed a lack of any relationship in women referred

for suspected sleep-disordered breathing during the third trimester of pregnancy. However this could be due to a low signal to noise ratio in breathing events during sleep in pregnancy.

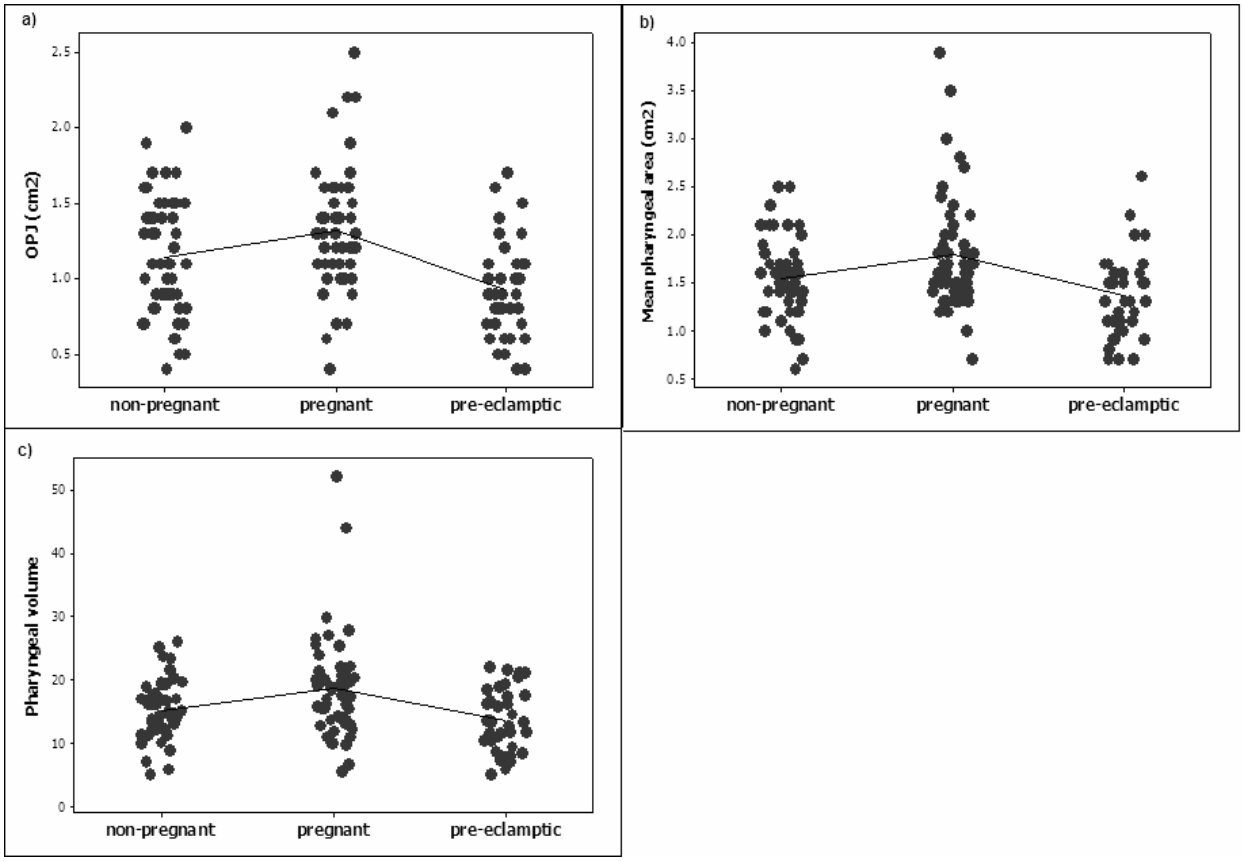
Regional fat deposition which infiltrates pharyngeal muscle tissue or soft tissue deposition in the neck and around UA may cause UA narrowing and symptoms of sleep-disordered breathing in pregnancy rather than generalized obesity (Mohsenin 2001, Izci et al 2003, chapter 5). Pien et al (2005) showed that neck circumferences increased during pregnancy, a finding which the current study confirmed and strengthened by showing a decrease in neck size postpartum. Schwab et al (1993b) have highlighted the importance of the lateral pharyngeal walls in the mediating UA calibre together with the tongue and soft palate in snorers. The predominant anatomic abnormality also can be an important factor underlying UA narrowing in pregnant women. In a recent study, physical examination showed that snoring pregnant women had abnormal oropharyngeal anatomy with a small oropharynx in the first trimester of pregnancy (Guilleminault et al 2004).

The UA narrowing may also result from increased progesterone level which increases vascular permeability, resulting in tissue oedema (Edwards et al 2005). In a pregnancy study, ENT examination also revealed nasal mucosal engorgement at six month of pregnancy (Guilleminault et al 2004). This may be due to increased circulating estrogen concentrations which lead to vasodilatation, particularly in the nasal vasculature. Both oedema and nasal obstruction can increase frequency of snoring and breathing pauses, decreasing UA dimension.

The discrepancies between the data presented in this chapter and chapter 5 were unexpected. It is true that the first study was a smaller one with a relatively small power for three way comparisons. This could have led to the production of rather uncertain results. In addition some confounding factors—social class, education, income etc, and also facial bony structure—which we either could not, or did not, control for (as explained in chapter 5) might have contributed to this unexpected result in the first study (chapter 5) and, thus, to discrepancy between the two studies.

Furthermore, a p value only gives information about whether a difference is likely to be statistically significant or not. It does not prove it is real or give the size. A p value of 0.05 is conventionally used as a cut off point. If we used a different p value such as 0.01, the statistical significance of our results would change. Data in the first study presented in chapter 5 were around 2 % level which is not very strong as regards multiple comparisons. When we look at our results by means of diagrams (Figure 6.2), even though there were statistically significant differences, there are no large differences in OPJ, mean pharyngeal area and volume between pregnant and non-pregnant women.

Figure 6.2 Comparisons of a) OPJ area b) mean pharyngeal area and c) pharyngeal volume of non-pregnant women, pregnant, and pre-eclamptic women



One could argue the more important measurement might be in the supine position due to gravity and the pressure around UA. Some women sleep in supine and lateral positions. In our first study (chapter 5) there was no difference in UA calibre between pregnant and non-pregnant women in the supine and lateral postures. Women with pre-eclampsia had narrower pharyngeal areas than the non-pregnant women. The OPJ also tended to be narrower in the women with pre-eclampsia than in the pregnant women.

In the first study (chapter 5), we originally aimed to look at whether pre-eclampsia had an effect on UA size. This study aimed to examine the effect of pregnancy on UA size. Therefore we set up a much bigger and much more powerful study to investigate this

question. In this study there were significant differences between UA sizes of pregnant and non-pregnant women. The results of the follow-up study also confirmed these findings, comparing UA size during third trimester of pregnancy and after delivery within the same group. Additionally, meta-analysis (please see chapter 9, figure 8.4) was performed combining data from the first and second studies. The results from meta-analysis were also in the same direction with this study as follow-up study was. Therefore we are confident about the reliability of our results.

In this study, systolic blood pressure was higher in pregnant women than non-pregnant women. Pregnant women who took part in the follow-up study also had higher systolic blood pressure in pregnancy than postpartum. Edwards and colleagues (2000b) found an association between UAs narrowing during sleep and blood pressure surges in women with pre-eclampsia. Another study by Edwards et al (2005) showed the marked fluctuations in nocturnal blood pressure as a result of apnoeic cycles, with systolic blood pressure increasing up to 170 to 180 mm Hg during the antenatal sleep studies in the last trimester of pregnancy. Our study extends these observations by indicating weak correlations between UA size during wakefulness and blood pressure in these groups, but it must be stressed that none explained more than 9% of the variance in blood pressure.

Women in the third trimester of pregnancy had higher Epworth Sleepiness Scale scores than in their pre-pregnancy and postpartum periods and felt less refreshed on wakening in the morning in the third trimester of pregnancy than in pre-pregnancy period. Pregnant women also had higher Epworth Sleepiness Scale scores than non-pregnant

women. That having been said, the mean Epworth Sleepiness Scale score of pregnant women did not reach the usual level for excessive daytime sleepiness derived from studies in normal adults (ESS >10) (Johns 1991, Johns 1994). Confirmation of this comes from a study by Pien et al (2005) which shows that Epworth Sleepiness Scale scores increased during pregnancy but the mean Epworth Sleepiness Scale score was 10 (SD 0.4) at the end of pregnancy. However, Baldwin et al (2004) reported that women were less likely to have an Epworth Sleepiness Scale score >10 and were more likely to report feeling unrested when compared to men. Therefore, it can be suggested that pregnant women are relatively sleepy. This is not surprising as difficulty sleeping in pregnancy is well documented (Bradley et al 1986, Kowall et al 1989, Lefcourt and Rodis 1996, Loube et al 1996, Edwards et al 2000b, Franklin et al 2000, Guilleminault et al 2000, Connolly et al 2001, Maasilta et al 2001, Izci et al 2003, Guilleminault et al 2004).

Our study has several limitations. Firstly, the results reported in this study were obtained during wakefulness. Measurements using this technique, however, correlate well with snoring and disturbed breathing during sleep (Bradley et al 1986, Martin et al 1995, Mohsenin 2001). Differences measured during wakefulness do not necessarily predict differences during sleep, but this technique has shown narrower airways in awake patients with OSAHS than in snorers (Hoffstein et al 1984, Bradley et al 1986, Martin et al 1995), and also shows that awake snorers have narrower UAs than non-snorers (Bradley et al 1986). Thus the results of acoustic reflection during wakefulness have been shown to predict differences in airway calibre and function during sleep (Hoffstein et al 1984, Bradley et al 1986, Martin et al 1995, Mohsenin 2001).

Secondly, the comparative study with healthy non-pregnant women had a cross-sectional design. There are always potential selection biases between the groups of subjects. A cross-sectional study cannot prove potential reasons and consequences, but only propose reasons when other confounding factors are controlled. In this study, the factors which may alter UA dimension were controlled including gender (White et al 1983, Martin et al 1997, Mohsenin 2001, Malhotra et al 2002), age (Martin et al 1997, Fogel et al 2005), obesity (Martin et al 1997, Peppard et al 2000a, Maasilta et al 2001, Welch et al 2002, Fogel et al 2003a, Lueng et al 2005), familial factors (Mathur and Douglas 1995b) and sleep state (Trinder et al 1997, O'Connor et al 2000, Thurnheer et al 2001). However, the non-pregnant group tended to have higher BMI ($p<0.059$) than pregnant group reported prior to pregnancy. An increased BMI in the non-pregnant group would bias against the findings in this study by predisposing to UA narrowing, snoring and apnoeas (Hoffstein et al 1984, Martin et al 1997, Maasilta et al 2001, Mohsenin 2001) in the non-pregnant group, so this cannot be a factor in our findings of the reverse.

The longitudinal aspect of the study with repeated measurement postpartum adds credence to our findings in the cross-sectional component. However, the potential recall bias may occur when pregnant women are asked at least 3 months later about their pre-pregnancy snoring, breathing pauses, refreshment, Epworth Sleepiness Scale scores but the main outcomes of the study were objective. Another limitation of this is that we failed to recruit 50 of the 100 women in the second part of the study after delivery. The women recruited did not differ from the decliners in terms of snoring or UA characteristics and we believe the observations of widening of UA calibre postpartum

are likely to be robust. Another limitation is the number of statistical comparisons performed. There were 24 comparisons in airway size and thus by chance alone 1 (24/20) significant difference would have been found at the p=0.05 level. In fact 7 differences were found and all in the hypothesised direction. Thus the large number of comparisons cannot account for the changes found. It must be noted that our blood pressure measurements were limited to single measurements in each subject and thus need to be interpreted with considerable care.

The study shows that pregnant women have statistically significant UA narrowing during the third trimester of pregnancy. It is likely that reduced UA calibre may contribute to the increased rate of snoring and sleep-disordered breathing in pregnancy. The further clinical significance of these airway calibre changes requires further study.

CHAPTER 7
SLEEP COMPLAINTS: SNORING AND DAYTIME SLEEPINESS IN PREGNANT AND PRE-ECLAMPTIC WOMEN

7.1 Introduction

Both snoring and sleepiness (Loube et al 1996, Franklin et al 2000, Guilleminault et al 2000, Lee et al 2000, Edwards et al 2002, Izci et al 2003, chapter 5, Lueng et al 2005, Pien et al 2005, Izci et al 2006, chapter 6) are common in pregnancy, but it is not clear whether these features are associated. I thus examined the association of snoring and sleepiness across groups of non-pregnant and pregnant women in this questionnaire-based study. The pregnant group was supplemented with women with additional women with pre-eclampsia as they have a higher rate of snoring (Franklin et al 2000, Izci et al 2003, chapter 5). I also assessed the relationship between predictive variables and pre-eclampsia.

7.2 Method

7.2.1 Subjects

●**Pregnant Women:** One hundred and ninety-seven healthy pregnant in the third trimester of their pregnancies attending a day assessment unit or admitted to the antenatal ward were consecutively considered for participation in this study (chapter 4). One hundred and ninety-four of them agreed. One hundred and sixty-seven participated to the study. The rest were excluded due to having twins (n=3), essential or gestational hypertension (n=7), diabetes mellitus (n=8), severe asthma (n=3) or insomnia (n=1), suspected periodic leg movement (n=1) or cystic fibrosis (n=1), or were pregnant less than 28 weeks (n=3). Four of them did not return the questionnaire for unknown reasons.

●Pre-eclamptic women: Ninety-three pre-eclamptic women including both primigravida and multigravida in the third trimester, attended a high risk clinic or admitted to the day assessment unit and the antenatal ward were approached. Ninety of them agreed to join the study and 82 of them actually took part in the study. The remaining 8 were excluded due to suffering from pre-existing essential hypertension (n=2), diabetes mellitus (n=2), or having twins (n=3) or abnormal foetus detected by ultrasound scan (n=1).

●Non-pregnant women: One hundred and seventy-seven non-pregnant women, who are advertisement respondents as explained in chapter 4, mainly hospital staff, were approached. One-hundred and sixty of them took part in the study. Nine of them were excluded due to being morbidly obese (n=2), older than 42 (n=4), suffering from hypertension (n=2) or a respiratory infection (n=1). Eight of them did not return back the questionnaires due to unknown reasons.

All subjects gave written informed consent to the study, which had the approval of the local ethical advisory committee.

7.2.2 Protocol

7.2.2.1 Questionnaires

All subjects, together with their partners, completed the standard sleep-wake questionnaires (appendix A, E, D and H), which were described and validation studies conducted in chapter 4. If subjects agreed to take part but had limited time to do so, a questionnaire and self-addressed stamped envelop was provided for both them and their partner, in order to allow them to send the questionnaires (for both) back at their

convenience. Criteria for snoring and breathing pauses were used as explained in chapter 4.

7.2.2.2 Measurements

For all women height, weight, and neck circumferences were recorded and blood pressure measured as delineated in chapter 4.

7.2.3 Statistical analysis

Comparisons were performed using the paired t-test for dependent samples and analysis of variance, followed by between-group comparisons using the Student–Neuman–Keuls multiple comparison test when appropriate. Logistic regression was used to analyze the relationship between snoring and sleepiness. The relationship between predictive variables and pre-eclampsia also was assessed using logistic regression. Such analysis aims to predict the relationship of a categorical dependent variable (in this case, pre-eclampsia/normal pregnancy) on the basis of continuous independent variables such as neck circumference, BMI, waist circumference, hip circumference and pre-pregnancy BMI. Chi-square and Pearson's correlation were used in the basic descriptive statistical analyses. Results are presented as mean with (±SD) or (±SEM). P values of 0.05 or less were taken as significant.

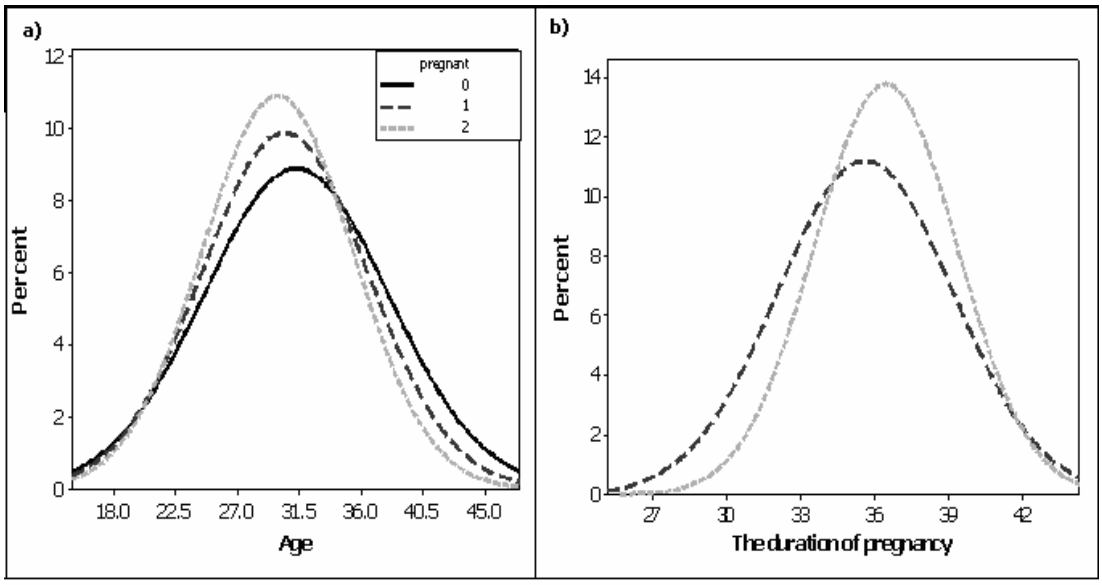
7.3 Results

7.3.1 Subject characteristics

In this study, 160 non-pregnant women, 167 pregnant, and 82 pre-eclamptic women were compared for mean age (31 (±SD 7), 30 (6) and 30 (6) yrs respectively).

Additionally, healthy pregnant and pre-eclamptic women were compared for mean duration of pregnancy (36 (±SD 3.6) and 36 (3) weeks respectively). These three groups were similar in mean age, and healthy pregnant women and pre-eclamtic women were similar in mean duration of pregnancy (Figure 7.1).

Figure 7.1 Comparisons of a) mean age between non-pregnant women, pregnant, and pre-eclamptic women and b) mean duration of pregnancy between healthy pregnant and pre-eclamptic women



There were also no significant differences between pregnant, pre-eclamptic and control women in terms of height, but pre-eclamptic women were heavier than pregnant and non-pregnant women and reported higher BMI than pregnant women before pregnancy (Table 7.1). Pre-eclamptic women had significantly larger neck circumferences than the healthy pregnant and non-pregnant women, and pregnant women also had larger neck circumferences than non-pregnant women (Table 7.1).

Table 7.1 Mean (±SD/SEM) of subjects' characteristics and blood pressure measurement

	Non-preg n=160	**Preg n=167**	**Pre-ecl n=82**	**Non-Preg vs Preg**	**Preg vs Pre-ecl**	**Non-preg vs Pre-ecl**	**P**
Height, m	1.64±0.1	1.65±0.1	1.64±0.1				>0.3
Weight pre-pregnancy, kg	65±11	64±13	68±12	>0.4	<0.05	<0.05	<0.05
BMI pre-pregnancy, kg/m2	24.4±4	23.6±5	25.3±4	>0.2	<0.05	>0.1	<0.03
NC, cm	33±2	34±2	36±3	0.05	<0.05	<0.05	<0.001
SBP, mmHg	108±1	116±1	140±2	<0.05			<0.001
DBP, mmHg	71±1	73±1	90±1	>0.1			<0.001

Abbreviations: SD = standard deviation; SEM = standard error of the mean; NC=neck circumference, BMI = body mass index; SBP = systolic blood pressure and DBP = diastolic blood pressure.

7.3.2 Snoring and breathing pauses

Neither the subject nor her partner reported knowing if the subject snored in nine percent of non-pregnant, 7% of pregnant and 13% of pre-eclamptic women. Of those who did know, thirty-two percent of non-pregnant, 55% of pregnant and 85% of pre-eclamptic women ($p<0.001$) were reported to be snorers (Table 7.2). Seventeen percent of snoring non-pregnant women, 35% of snoring pregnant women and 59% of snoring pre-eclamptic women were habitual snorers ($p<0.001$). In contrast, the rates of snoring in non-pregnant women were not different from those of the pregnant and pre-eclamptic women prior to becoming pregnant ($p>0.7$). In the same way, only 10% of both the pregnant and pre-eclamptic women reported that they snored habitually before pregnancy (compared to habitually snoring non-pregnant women, $p>0.1$) (Table 7.2).

Table 7.2 Percentage of symptoms regarding snoring and breathing pauses reported by both the women and partners

	Non-preg n=160	**Preg n=167**	**Pre-ecl n=82**	**P**
Snoring in last month	32%	55%	85%	<0.001
Habitual snoring in last month	17%	35%	59%	<0.001
Breathing Pauses in last month	6%	18%	35%	<0.001
Snoring in pre-preg period	32%	27%	36%	>0.7
Habitual snoring pre-preg period	17%	10%	10%	>0.1
Breathing Pauses in pre-preg period	6%	13%	12%	>0.2

Twenty-seven percent of non-pregnant, 32% of pregnant and 42% of pre-eclamptic women, and their partners, did not know if the women had breathing pauses. Six percent of non-pregnant, 18% of pregnant and 35% of pre-eclamptic women were reported to have breathing pauses ($p<0.001$) (Table 7.2). Thirteen percent of pregnant and 12% of pre-eclamptic women were reported to have breathing pauses prior to becoming pregnant ($p>0.2$).

All habitually snoring pre-eclamptic women and their partners reported that they had breathing pauses (compared to non-habitually snoring pre-eclamptic women, $p<0.001$). However, there was no significant relationship regarding breathing pauses when habitually snoring pregnant and non-pregnant women were compared to non-habitually snoring pregnant and non-pregnant women (both $p>0.1$).

7.3.3. Daytime sleepiness, refreshment and depression

Healthy pregnant women and those with pre-eclampsia were sleepier than non-pregnant women on average (Table 7.3). Sleepiness (ESS score≥11) was reported in 23% of pregnant women, 15% of pre-eclamptic women and 12% of non-pregnant women ($p<0.04$). Women with pre-eclampsia felt less refreshed than healthy and non-pregnant women (Table 7.3). No significant correlation was found between Epworth Sleepiness Scale score and either age, pre-pregnancy BMI or neck circumference in the three groups.

Table 7.3 Mean (±SEM) of sleepiness and refreshment between groups

	Non-prg	**Preg-nant**	**Pre-eclam**	**Non-preg vs preg**	**Preg vs Pre-ecl**	**Non-preg vs Pre-ecl**	**P**
ESS in last month (women)	5.9±0.4	7.3±0.4	6.7±0.6	<0.05	>0.3	<0.05	<0.001
ESS in last month (partner)	5.8±0.5	7.1±0.4	6.4±0.5				>0.1
Refreshment in last month	3.1±0.1	2.8±0.1	2.6±0.1	>0.06	<0.05	<0.05	0.001

Abbreviations: SEM = standard error of the mean; ESS = Epworth sleepiness scale

Fifteen non-pregnant, 16 pregnant and 12 pre-eclamptic women reported that they had had depression before ($p>0.3$). None of them cited that they had depression at the time of the study.

7.3.4 Comparison of snoring, daytime sleepiness and refreshment between pre-pregnancy and third-trimester of pregnancy

The frequency of snoring and the Epworth Sleepiness Scale scores reported by pregnant women, pre-eclamptic women and their partners significantly increased by the last month of pregnancy. Refreshment ratings significantly decreased in both pregnant and pre-eclamptic women by the last month of pregnancy (Table 7.4).

Table 7.4 Comparisons of snoring, daytime sleepiness and refreshment between pre-pregnancy and third-trimester of pregnancy period [Mean (±SEM)]

	Pregnant Women		**P**	**Pre-eclamptic Women**		**P**
	Pre-preg	**Third Trimester**		**Pre-preg**	**Third trimester**	
Pregnant women's and their partner's ratings combined						
Snoring (%)	27	55	<0.001	36	85	<0.001
Habitual snoring (%)	10	35	<0.001	10	59	<0.001
Breathing pause (%)	13	18	>0.3	12	35	<0.02
Pregnant womens' rating						
ESS	4.2±0.3	7.3±0.4	<0.001	3.4±0.5	6.5±0.6	<0.001
Refreshment	3.7±0.1	2.8±0.1	<0.001	3.7±0.1	2.6±0.1	<0.001
Partners' rating						
ESS	4.8±0.3	7.1±0.4	<0.001	4.2±0.5	6.4±0.5	0.002

For abbreviations, see Table 7.3.

7.3.5 Correlation between snoring and sleepiness

There was a significant positive relationship across all subjects between reported snoring and Epworth Sleepiness Scale score when examined by logistic regression (r=0.13,

p=0.002). There was also a similar significant correlation across all participants between habitual snoring and Epworth Sleepiness Scale score (r=0.09, p<0.02). When data were controlled for age, BMI and neck circumference, there was still a significant relationship between reported snoring and Epworth Sleepiness Scale score (r=0.2, p=0.001). When previous depression status was controlled along with age, BMI and neck circumference, the correlation was 0.25 (p<0.02) in all participants. Within the pregnant group (healthy pregnant and pre-eclamptic women) there was also a significant relationship between snoring and Epworth Sleepiness Scale score when controlling for age, BMI and neck circumference (r=0.1, p<0.05).

7.3.6 Blood pressure and snoring

Healthy pregnant women's systolic blood pressure was significantly higher than that of non-pregnant women (p<0.05) (Table 7.1). When the healthy pregnant group was divided into snoring and non-snoring groups, snoring pregnant women's systolic and diastolic blood pressure were also significantly higher than those of non-pregnant women (systolic: 118 ±SEM 1 vs. 108±2 mmHg; P<0.05, diastolic:74±1 vs. 71±1 mmHg; p<0.05, respectively).

7.3.7 The relationship between predictive variables and pre-eclampsia

In a univariate logistic regression analysis, neck circumference, BMI, waist circumference, hip circumference and pre-pregnancy BMI, were significantly correlated with pre-eclampsia (Table 7.5). When a multiple logistic regression model was performed with these independent variables, this showed that neck circumference, BMI and waist circumference were associated with pre-eclampsia. However, hip

circumference and pre-pregnancy BMI were not independently associated with pre-eclampsia (Table 7.6).

Table 7.5 Explanatory variables associated with pre-eclampsia (univariate logistic regression analysis)

Variable	Odds ratio	95% CI		p
NC	1.69	1.45	1.99	<0.0001
Waist C	1.04	1.01	1.0752	<0.01
Hip C	1.05	1.01	1.0767	0.05
BMI	1.15	1.08	1.2298	<0.0001
Pre-pregnancy BMI	1.09	1.02	1.1596	<0.02

Abbreviations: CI=confidence interval, NC=Neck circumference, C=circumference

Table 7.6 Explanatory variables associated with pre-eclampsia (multiple regression analysis)

Variable	Odds ratio	95% CI		p
NC	2.14	1.59	2.88	<0.0001
Waist C	0.87	0.79	0.95	0.001
Hip C	0.95	0.88	1.02	0.13
BMI	1.35	1.05	1.65	<0.02
Pre-pregnancy BMI	0.88	0.74	1.04	0.13

For abbreviations, see Table 7.5.

7.4 Discussion

This study confirms that snoring, daytime sleepiness and unrefreshing sleep are significantly more common in healthy pregnant women and pre-eclamptic women in the

last trimester of pregnancy. This study extends previous observations by showing that in both the pre-eclamptic and healthy pregnant groups the rates of snoring prior to pregnancy were similar to those of the non-pregnant women, suggesting that the high rates of snoring in pre-eclampsia are acquired, not pre-morbid. Another important finding in this study is that although snoring, breathing pauses and sleepiness are more common in pregnant women, the correlation between snoring and sleepiness is weak, suggesting that sleepiness in pregnancy may be mainly largely due to factors other than UA obstruction.

Our findings on sleepiness are compatible with results in other studies which indicated that 52% of pregnant women at the sixth month (Guilleminault et al 2000) and 45.5-65% at the end of pregnancy complained of daytime sleepiness (Franklin et al 2000, Pien et al 2005). These results concur with the 23% of healthy pregnant women, in our study, who had Epworth Sleepiness Scale scores of 11 or higher. Contrary to these findings, Loube et al (1996) reported that Epworth Sleepiness Scale scores did not change with pregnancy. In the current study, only 15% of pre-eclamptic women had Epworth Sleepiness Scale scores of 11 or higher.

This study suggests that the quality of sleep declines during pregnancy. Previous studies have reported that sleep efficiency decreased during pregnancy due to increases of duration and frequency of awakening in pregnant and pre-eclamptic women (Driver and Shapiro 1992, Edwards et al 2000a, Lee et al 2004). An important factor impairing sleep quality during the third trimester of pregnancy could be snoring (Franklin et al 2000, Guilleminault et al 2000, Lueng et al 2005, Izci et al 2003 and 2006, chapter 5 and 6).

The combinations of pregnancy-induced changes such as oedema (Edwards et al 2005, Pilkington et al 1995), a 15-25% reduction in FRC (Gee et al 1967, Craig and Toole 1975, Holdcroft et al 1977) and weight gain (Franklin et al 2000, Maasilta et al 2001, Lueng et al 2005, Pien et al 2005), may predispose women to snore and experience UA obstructive events during pregnancy (Elkus and Popovich 1992, Loube et al 1996, Edwards et al 2000a, Franklin et al 2000, Guilleminault et al 2000). The current study confirmed previous reports. It shows snoring to be common in pregnant women (55%), especially those who are pre-eclamptic (85%), compared to non-pregnant women (27%) (Kowall et al 1989, Lefcourt and Rodis 1996, Loube et al 1996, Edwards et al 2000b, Franklin et al 2000, Guilleminault et al 2000, Connolly et al 2001, Maasilta et al 2001, Lunegwt al 2005, Pien et al 2005). Thirty-five percent of snoring pregnant women, 59% of snoring pre-eclamptic women and 10% of non-pregnant women were habitual snorers. Our results on habitual snoring in 35% of pregnant women were broadly similar to frequent snoring figures in previous studies which showed: 23% (Franklin et al 2000), 49% (33% often and 16% always) (Loube et al 1996) of pregnant women snored frequently. In the same way, the percentage of reported snoring including occasional snoring (%55) confirmed previous studies' findings: 48% (Franklin et al 2000), 75 % (Loube et al 1996), 52% (Guilleminault et al 2000) and 44% (Leung et al 2005) of pregnant women snored.

Another reason for poorer sleep quality might be breathing pauses which accompany snoring. In the present study, breathing pauses tended to increase during the last trimester of pregnancy in both healthy pregnant and pre-eclamptic women. These results contrast with those of Brownell et al (1986) who found a decrease in the

frequency of apnoeas during pregnancy. The current study showed a higher prevalence of breathing pauses reported by pregnant and pre-eclamptic women and their partners than for non-pregnant women. However, the current data are limited by 27–42% of each group stating they did not know if they had breathing pauses, but our data are compatible with results from earlier studies. Pien at al (2005) reported that 1.3% of 155 pregnant women reported regular (≥ 3 times/week) apnoeic episodes when initially assessed, this number reached to 15% at 28 to 29 weeks of pregnancy. Two studies preformed with pre-eclamptic women also indicated that pre-eclamptic women commonly experienced episodes of non-apnoeic upper-airway flow limitation during sleep (Edwards et al 2000b, Connolly et al 2001). Furthermore, case reports indicated that women with mild or moderate sleep apnoea prior to pregnancy experience a worsening of their condition during pregnancy (Kowall et al 1989, Lefcourt and Rodis 1996, Roush and Bell 2004).

In this study, the weak correlation (although statistically significant) between sleepiness and snoring may indicate either poor subjective assessment by participants of their or their partners' sleepiness level, or inaccuracy of Epworth Sleepiness Scale in this particular age group and female gender (pregnant subjects). There are contrary findings concerning whether age and gender have an effect on Epworth Sleepiness Scale score. Chervin and Aldrich (1999) showed that the male gender had a greater influence on the Epworth Sleepiness Scale score compared to objective measures of sleep-disordered breathing severity even after controlling confounding variables. They studied sleepiness in 237 patients, mean aged 44 years, with OSAHS of mild to moderate severity (138 men and 98 women) using the Epworth Sleepiness Scale, which was the same

instrument used for this study (Chervin and Aldrich 1999). Baldwin et al. reported that women were less likely to have an Epworth Sleepiness Scale score >10 and were more likely to report feeling unrested (Baldwin et al 2004). They enrolled middle-aged or older participants who had previous risk factors for cardiovascular disease or had chronic cardiovascular disease (Baldwin et al 2004). Contrary to these findings, Mohsenin (2001) recruited a similar subject group with AHI ≥5 (78 men and 52 women, mean aged 48), and showed that both genders reported similar degrees of daytime sleepiness as determined by Epworth Sleepiness Scale. As explained above, the features of the subjects of these studies are different from ours. Edwards et al (2000b) found that even pre-eclamptic women did not have AHI >10. Studies recruiting younger subjects, including snorers and non-snorers, reported no significant gender effect on Epworth Sleepiness Scale scores. For example, Johns and Hocking (1997) recruited 331 Australian workers aged 22–59 years (267 men and 64 women) using the Epworth Sleepiness Scale, and found that there was no difference between men's and women's Epworth Sleepiness Scale scores. Mean Epworth Sleepiness Scale score for men was 5.8 ±SD4 and for women was 5.7±3. In another study with a sample of 188 ostensibly healthy young subjects from the UK, it was reported that Epworth Sleepiness Scale score were similar in males (5±SD3) and females (4±3) (Parkes et al 1998). In our study, pregnant and pre-eclamptic women's mean Epworth Sleepiness Scale before pregnancy (respectively 4.2 ±SEM 0.3 and 3.4±0.5) and healthy non-pregnant women's mean Epworth Sleepiness Scale (5.9±0.4) were similar to mean Epworth Sleepiness Scale scores in previous studies. Furthermore, in a validation study of Epworth Sleepiness Scale, Johns (1991) obtained the same mean Epworth Sleepiness Scale score (5.9

±SED2.2) from 30 hospital employees enrolled as a control group (similar to our controls) (14 male/16 female, mean age=36).

Regarding pregnant women, Loube et al. (1996) also used Epworth Sleepiness Scale to assess sleepiness in pregnant women, compared to age-matched control women. However, the mean Epworth Sleepiness Scale score was not different between the groups (9.8 ±SD 3.9 in pregnant vs. 9.2±3.2 in non-pregnant women), although both groups were mildly sleepy. In contrast, Pien et al (2005) showed using Epworth Sleepiness Scale that the degree of daytime sleepiness (8.6 ±SD 0.3 vs 10.2±0.4, p=0.0003) increased significantly from the first trimester to the end of pregnancy. There is no particular published study which evaluated the reliability or validity of Epworth Sleepiness Scale in women, and especially not in pregnant/pre-eclamptic women. However, a validation study of Epworth Sleepiness Scale which was performed for the studies in this thesis showed that test-retest reliability and internal consistency of Epworth Sleepiness Scale for women are good (see chapter 4).

Sleep symptoms, including tiredness, feeling unrested, low energy, lack of vigor, and fatigue, used to explain daytime sleepiness, can also be associated with depression rather than snoring or breathing pauses (Chervin 2000). Therefore, depressive symptoms could confound Epworth Sleepiness Scale scores. In the current study, participants answered a question about depression status. Fifteen non-pregnant, 16 pregnant and 12 pre-eclamptic women had depression history previously, but none of them reported that they had depression at the time of the study. When depression status was included along

with age, BMI and neck circumference, the correlation between snoring and Epworth Sleepiness Scale score did not alter significantly.

In this study, logistic regression analyses showed that neck circumference, waist circumference and BMI in the third trimester of pregnancy may be independent predictors for pre-eclampsia. These factors also have been found to be associated with sleep-disordered breathing (Davies and Stradling 1990, Deegan and McNicholas 1996, Mortimore et al 1998, Franklin et al 2000, Maasilta et al 2001, Edwards et al 2002). These may also explain high percentage of snoring in pre-eclamptic women.

Limitations of the present study include its questionnaire-based character and the lack of objective assessment of snoring and daytime sleepiness using more objective techniques such as PSG and MSLT. However, PSG also has significant limitations resulting in one night's data being used, whereas we used data (albeit softer) from many nights. In our experience, patients with pregnancy and pre-eclampsia are reluctant to undergo PSG and may sleep very poorly when monitored. This experience, which caused us to alter our original intention to measure breathing during sleep, will be detailed in the next chapter. Another limitation was that the non-pregnant women were mainly hospital staff, whereas it would have been more thorough to recruit healthy volunteers from the general population.

This study indicates increased snoring, breathing pauses and sleepiness in the third trimester of pregnancy, especially in patients with pre-eclampsia. However, the study suggests that sleepiness is not due to snoring or breathing pauses.

CHAPTER 8
SLEEP DISORDEREDBREATHING IN PREGNANCY AND PRE-ECLAMPSIA (original intention of this thesis)

8.1 Introduction

In addition to the objectives covered in the previous chapters, this thesis also originally intended to study the following hypotheses:

1. that UA narrowing during sleep is more severe in patients with pre-eclampsia

2. that nasal CPAP can significantly reduce overnight diastolic blood pressure in patients with pre-eclampsia by 5 mmHg compared with usual therapy

We had difficulty making progress with these hypotheses. There are a number of reasons for this including:

1. Fewer pre-eclamptic patients were available to recruit due to the fact that at the beginning of this study Simpson Centre for Reproductive Health of the Royal Infirmary of Edinburgh moved to a new hospital (New Royal Infirmary of Edinburgh), which resulted in the loss of antenatal beds and meant that patients with pre-eclampsia were no longer being kept in hospital overnight.

2. The new hospital is outside the city centre which makes patients' transportation difficult and undesirable if they do not need to go to the hospital.

3. The pre-eclamptic women were unwilling to take part in the study because of its complexity. Particularly troublesome were the problems involving difficulty in sleeping and difficulty in going to the rest room during the night.

4. The pre-eclamptic women whom I tried to recruit were nervous about their condition and their unborn baby's health. Because of these difficulties and concerns, they chose not to be involved in the study.

5. Pre-eclamptic women who agreed to take part in the study were often induced or sometimes discharged or their condition was too poor for them to take part in the study.

6. Technical problems were encountered, such as flash memory card or broken nasal prongs, which are essential to score inspiratory flow limitation.

7. Resistance was encountered from some amongst the midwifery staff to this research.

8.2 Methods

8.2.1 Intended sample size and power

To show a change of 5mm Hg in diastolic blood pressure after treatment, 20 patients are required in each of the CPAP and control groups, which gives 90% power at the 5% level, using data from our department (Faccenda et al 2001). Thus, the required sample size for this study was 40 patients with positive findings on the diagnostic night and 20 consecutive healthy pregnant women in 3rd trimester of pregnancy.

8.2.2 Subjects

●Healthy pregnant women: Twenty-eight pregnant women in third trimester of pregnancy were approached and 6 of them were recruited. The remaining twenty-two healthy pregnant control women either refused (n=19) or did not show up at the study time.

●Pre-eclamptic women: Sixty-eight pre-eclamptic women in third trimester of pregnancy were approached and 15 of them agreed to take part in the study. Fifty-three pre-eclamptic women either refused to take part or were induced or discharged before

the evening of presentation. Two pre-eclamptic women did not want to continue the sleep study at most 2 hours later after commencing the study. One woke up screaming after noticing all the electrodes. Three women's data were not usable for technical reasons. One could not sleep during the whole night. One wanted to leave the study after wiring up. Only 6 patients' and 6 healthy women's data were usable.

8.2.3 Measurements

Overnight PSG studies were performed at either the Department of Sleep Medicine (n=10) or Simpson Centre for Reproductive Health (n=10) of the New Royal Infirmary of Edinburgh.

Patients with pre-eclampsia and healthy pregnant women of similar gestation (third trimester) without pre-eclampsia had overnight full PSG recording using Siesta Wireless Portable Patient Monitoring System (Compumedics, Melbourne, Australia), and 24 hour blood pressure recording by a Space Labs system. Of course those who we were unable to recruit did not undergo this set of procedures.

- **Nocturnal PSG:** Measurements included central and frontal electroencephalograms (EEG, C3-C4, CZ-PZ, F3-FP1, and F4-FP2), two electrooculograms (EOGs), submental and right and left tibial electromyograms (EMGs), and the electrocardiogram (ECG) and body position recorded using a body sensor.

Respiratory monitoring in the PSG comprised airflow via a nasal cannula, snoring noise

via a microphone, oxygen saturation using an integrated oximeter and abdominal and respiratory efforts recorded using chest and abdomen bands.

All signals were recorded on Siesta Wireless Portable Patient Monitoring System (Compumedics, Melbourne, Australia), which allows the monitoring and diagnosis of sleep conditions in hospital or the home environment.

Data were either stored to compact flash memory storage (144Mb) if patients were recruited in Simpson Centre for Reproductive Health, Royal Infirmary or to the host computer via an internal radio transmitter which communicates with computer networks, if patients were recruited in the Department of Sleep Medicine. The data from flash memory storage were moved on the computer for further analysis.

Those with pre-eclampsia showing evidence of UAs obstruction during sleep would be randomised to undergo either a full-night CPAP titration study using an automated pressure setting device (Auto Set; ResMed, Sydney, Australia) or the usual conventional therapy on the second night and 24 hour blood pressure would be again recorded. Any patient in whom there is a change in the anti-hypertensive medication between the first and second night would be excluded from the study. However, only two women with pre-eclampsia agreed to continue for the treatment night and next day one of them had to be induced. The other woman asked to end the CPAP treatment after 1 1/2 hours. The rest did not want to continue a second night.

● **Ambulatory Blood Pressure Monitoring;** All women were fitted with a

lightweight microprocessor to save the blood pressure data via an arm cuff (Ultralite ABPM; SpaceLabs Medical, Redmond, WA) from 9 pm to 7 am during sleep study and treatment night (only pre-eclamptic women). The ambulatory blood pressure monitoring (ABPM) module weighs 347 gr, and can be carried on a belt or shoulder strap, connecting to the arm cuff via a rubber hose. An appropriate cuff size was fitted to the left upper arm of women. The monitor was programmed to record systolic blood pressure, diastolic blood pressure, and mean arterial pressure every 2 hours.

8.2.4 Analysis of sleep stages and respiratory events

I was blinded to the subjects' details.

●**Sleep Staging:** Sleep staging was performed from EEG, EOG and EMG according to recognized criteria of Rechtschaffen and Kales (1968). It is based on 30-s epochs. An epoch is scored as sleep when 15 seconds or more of any sleep stage occupies the page.

●**Analysis of respiratory events:** To assess UA resistive events during sleep, nasal airflow was carefully analysed. UA resistive events were described as a plateauing of inspiratory nasal flow with increasingly negative pleural pressure swings for 2 breaths or more compared with the preceding baseline in the absence of hypopnoea (Rees et al 2000). The end of events was indicated by a restoration of pleural pressure to the sleeping baseline and a rounded flow contour (Rees et al 2000).

For this analysis, nasal flow signals were downloaded from the Compumedics Replay

program as European data files (EDF). In scoring, I specified periods of inspiratory flow limitation occurring in the absence of hypopnoeas from plateauing of inspiratory nasal flow according to the above definition in each patient while checking snoring position, chest and abdomen movements, and oxygen saturation. A power spectral density for each of these was then produced by Fast Fourier Transformation (FFT) which is a mathematical technique that converts digital information from the time domain to the frequency domain for rapid spectral analysis. These data were then stored as numbers in text files and transferred to the Microsoft Excel database. For further analysis appropriate data were moved to SPSS program.

8.2.5 Statistical Analysis

Comparison between pre-eclamptic and pregnant women was performed using Mann-Witney test. Results are expressed as median (and inter-quartile range [IQR]) values. P values of less than 0.05 were considered significant.

8.3 Results

8.3.1 Subject Characteristics

The median duration of pregnancy was 36 weeks (IQR 38-39) in the pregnant group, and 33 weeks (IQR 35-38) in the pre-eclampsia group (p=0.16). The pregnant and pre-eclamptic women did not differ in terms of age or height, or pre-pregnancy weight, BMI, pregnancy weight, pregnancy BMI or waist/hip ratio (Table 8.1). There was only a significant difference between the pregnant women and the pre-eclamptic women in measured neck circumferences.

Table 8.1 Characteristics of subjects studied (median, IQR)

	Pregnant (n =6)	**Pre-eclamptic (n =6)**	**P value**
Age, yrs	34(29-37)	32(29-36)	0.52
Height, m	1.63 (1.60-1.69)	1.65 (1.62-1.68)	0.64
Weight (pre-pregnancy), kg	69(63-76)	64 (56-81)	0.81
BMI (pre-pregnancy), kg/m^2	23(21-25)	22 (23-30)	0.81
Weight (pregnancy), kg	62(57-68)	79 (68-98)	0.18
BMI (pregnancy), kg/m2	27(24-29)	29(26-35)	0.22
NC, cm	33.5(32-34)	38(35-41)	0.02
Waist/hip ratio	0.98 (0.95-1)	0.97 (0.94-1)	0.33

Abbreviations: IQR= inter-quartile range, BMI = body mass index, NC=neck circumference.

8.3.2 Sleep related data

Sleep related data for each subject are presented in table 8.2. Sleep onset latency was significantly longer in pre-eclamptic women but there were no significant differences regarding total sleep time and sleep period time between groups. Sleep efficiency was slightly better in healthy pregnant women than pre-eclamptic women. However sleep efficiency, stage 1, 2 and 3, and REM sleep were not statistically significant between groups. Healthy pregnant women significantly slept more in stage 4 than pre-eclamptic women (Table 8.4).

Table 8.2 Sleep-related data for each subject

Subjects No	SPT min	TST min	SOL min	SE %	Stage1 min	Stage2 min	Stage3 min	Stage4 min	REM min
Healthy pregnant women									
1	436.23	366	15	83.90	10.50	263.00	20.50	14.00	62.00
2	447.76	360	18	80.40	21.00	255.00	36.00	8.00	40.00
3	423.61	366	2	86.40	9.50	199.50	24.50	45.50	91.00
4	357.35	275	27	76.90	9.50	142.50	21.00	52.00	73.00
5	221.46	136	21	61.50	2.00	84.00	19.50	28.00	13.50
6	462.73	251	36	54.20	8.00	140.50	29.00	51.50	28.50
Pre-eclamptic women									
1	221.00	145	22	65.70	6.00	112.50	20.00	24.00	0.00
2	456.59	374	45	82.00	9.50	273.00	31.00	2.50	68.50
3	462.96	150	141	32.40	7.50	106.00	5.00	2.50	4.50
4	376.66	323	49	85.70	7.00	260.00	35.00	11.00	24.50
5	278.91	194	76	69.70	7.50	167.00	6.50	.00	23.00
6	434.78	300	25	69.00	17.50	168.00	54.00	11.00	50.00

Abbreviations: No=subject number, SPT=sleep period time, TST= total sleep time, SOL=Sleep onset latency, SE=Sleep efficiency, REM=Rapid eye movement

8.3.3 Data on respiratory events, oxygenation during sleep and blood pressure

Respiratory events, oxygenation and blood pressure data for each subject are presented in table 8.3. Apnoeas and hypopnoeas were slightly more frequent in pre-eclamptic women and pre-eclamptic women desaturated more than healthy pregnant women but these were not statistically significant (Table 8.4). The average diastolic, systolic blood

pressure and mean arterial pressure during sleep were higher in pre-eclamptic women than healthy pregnant women (Table 8.4).

Table 8.3 Data on respiratory events, oxygenation during sleep and blood pressure for each subject.

Subjects No	AHI Hr sleep	IFLI Hr sleep	LowestSaO_2 min	AvDeO_2 %	AvSDB mmHg	AvDBP mmHg	Avmap
Healthy pregnant women							
1	8.10	37.80	90.00	.00	112	68	84.0
2	7.80	55.70	90.00	4.00	110	73	86.0
3	1.30	49.10	94.00	.00	119	69	86.0
4	17.00	25.80	91.00	.00	99	61	74.0
5	0.80	73.90	.	.	119	74	.
6	2.30	8.20	94.00	3.00	118	72	86.0
Pre-eclamptic women							
1	17.40	39.10	94.00	3.00	151	95	98.0
2	8.00	23.40	90.00	4.00	145	89	119.0
3	7.60	48.00	93.00	3.00	133	87	111.0
4	29.90	36.60	90.00	3.00	143	71	101.0
5	7.60	13.50	93.00	3.00	130	88	99.0
6	13.40	47.00	94.00	2.00	141	89	100.0

Abbreviations: No=subject number, AHI=apnoea-hypopnoea index, IFLI=inspiratory flow limitation index, LowestSaO_2 = lowest oxygen saturation, AvDeO_2= average oxygen desaturation, AvSBP= average systolic pressure, AvDBP = average diastolic pressure, Avmap = average mean arterial pressure

Table 8.4 Sleep-related data, respiratory events, oxygenation during sleep and blood pressure between two groups (median, IQR)

	Pregnant (n =6)	**Pre-eclamptic (n =6)**	**P value**
SPT (Min)	323 (430-452)	264(406-458)	0.94
TST (Min)	217 (222-336)	247(149-335)	0.69
SOL (Min)	19(12-29)	24(47-92)	0.03
Sleep efficiency %	79(60-85)	57 (70-83)	0.63
Stage 1 (Min)	10(7-13)	7(7.5-11.5)	0.33
Stage 2 (Min)	127(171-257)	111(167-263)	0.87
Stage 3 (Min)	23 (20-31)	26 (6-40)	0.87
Stage 4 (Min)	37(13-52)	2(7-14)	0.02
REM (min)	9(3-17)	14(11-24)	0.20
AHI Hr sleep	6(1-10)	11 (8-21)	0.15
IFLI Hr sleep	44 (21-60)	38(21-47)	0.42
Lowest O_2 saturation	91(90-94)	93(90-94)	0.84
Average O_2 Desaturation	0(0-4)	3(2.75-3.25)	0.21
Average Diastolic BP, mmHg	71 (66-73)	88 (83-100)	0.016
Average Systolic BP, mmHg	115 (107-119)	136(132-142)	0.004
Average mean arterial pressure, mmHg	82(79-86)	103(100-113)	0.006

Abbreviations: SPT=sleep period time, TST= total sleep time, SOL=Sleep onset latency, SE=Sleep efficiency, REM=Rapid eye movement, AHI=apnoea-hypopnoea index, IFLI=inspiratory flow limitation index, BP = blood pressure

8.4. Discussion

The present data indicate that inspiratory flow limitation, AHI during sleep are not significant between healthy pregnant and pre-eclamptic women in contrast to our previous finding showing that pre-eclamptic women have narrower UA size than healthy pregnant women. Even though in this study, pre-eclamptic women have larger neck circumferences (which may be associated with local fat deposition on the UA) than healthy pregnant women as we found in our previous study, this unexpected result occurred probably due to an insufficient number of subjects. As mentioned, in sample size and power calculation our aim was to recruit 40 pre-eclamptic women and 20 healthy pregnant women. In this study we did not even come close to quarter of this number due to many reasons which were mentioned above.

There are no randomised controlled trials to show the effect of CPAP on sleep-disordered breathing and blood pressure in pre-eclampsia. Such trials are essential if CPAP treatment is intended to be used for blood pressure treatment in pre-eclamptic women. Perhaps a multi-centred randomised controlled trial could be performed using the same criteria, as it is difficult to recruit that many patients in one hospital.

CHAPTER 9
CONCLUSIONS AND FUTURE WORK

The studies presented in this thesis aimed to study the effect of pregnancy and pre-eclampsia on the size of UAs. UA calibre in the awake state was measured using acoustic reflection technique on pregnant, pre-eclamptic and non-pregnant women. The findings of the studies indicated that the UAs of pregnant women decrease in the third trimester of pregnancy, when compared both to non-pregnant and postpartum women. Furthermore evaluation of the oropharyngeal area has demonstrated that pre-eclamptic women have narrower UA than healthy pregnant women. Additionally the studies in this thesis indicated that the features of sleep-disordered breathing such as snoring are prevalent in the third trimester of pregnancy. These results suggest that UA narrowing is the mechanism underlying the occurrence of snoring in pregnant women. This contributes to understanding of the increased prevalence of sleep-disordered breathing in pregnancy.

The study of UA size in pregnancy and pre-eclampsia (chapter 5) showed that women with pre-eclampsia had significantly narrower pharynxes when seated and supine than the non-pregnant and healthy pregnant women. However, the pregnant women had wider UAs compared with the non-pregnant women in the sitting position. This was despite the fact that pregnant women snored much more than non-pregnant women. Many reasons could lead to these unexpected results as mentioned in chapter 5. This counter-intuitive result could be spurious due to the large number of statistical analyses performed (56) and also the power of this study decreased due to a 3 way statistical comparison. Possible confounding factors not controlled for in the study were, for

example, UA abnormalities and the social class. Thus, a second study was performed with a large-scale 2-group comparison of UA size in pregnant and non-pregnant women. We also included a follow-up of the pregnant women postpartum to get more evidence on the effect of pregnancy on the UA. Additionally, I performed a meta-analysis including UA data from all 150 non-pregnant and 150 pregnant subjects studied in both studies to see whether there is a difference in groups overall (Table 9.1). The findings from the second study (chapter 6) and meta-analysis clarified the confusion over whether UA narrowing occurs in the third trimester of pregnancy or not.

This second study showed that pregnant women did have significantly narrower airways than non-pregnant women. It also showed that women had narrower airways during the third trimester of pregnancy than postpartum. Meta-analysis also showed that OPJ in supine and mean pharyngeal area in supine and lateral positions were narrower in pregnant women compared to non-pregnant women in third trimester of pregnancy (Table 9.1). In the seated position, there were no significant changes between pregnant and non-pregnant women. However, our main interest was the supine position; this is due to many reasons such as gravity, tissue pressure and loss of muscle tone due to sleep (Fouke and Strohl 1987, Deegan et al 1995) which may likely cause UA narrowing in the supine or lateral positions rather than the seated position.

Table 9.1 Meta-analysis of UA measurement from 150 pregnant and 150 non-pregnant women

	Non-pregnant (n =150)	Pregnant (n =150)	Differences		P value
			Mean	95% CI	
Upper airway: seated					
OPJ, cm^2	1.30(0.04)	1.28(0.03)	0.02	-0.08 to 0.12	0.67
CSA.mean, cm^2	1.74(0.04)	1.73(0.04)	0.01	-0.11 to 0.13	0.87
Vp, cm^3	18.42(0.56)	18.61(0.53)	-0.19	-1.71 to 1.33	0.80
Upper airway: supine					
OPJ, cm^2	1.10(0.03)	1.03(0.03)	0.08	0.00 to 0.15	0.05
CSA.mean, cm^2	1.56(0.032)	1.44(0.03)	0.11	0.03 to 0.20	0.01
Vp, cm^3	16.48(0.44)	15.37(0.43)	1.11	-0.10 to 2.33	0.72
Upper airway: Lateral					
OPJ, cm^2	1.18(0.03)	1.12(.03)	0.06	-0.02 to 0.13	0.15
CSA.mean, cm^2	1.63(0.03)	1.54(0.04)	0.10	-0.001 to 0.19	0.05
Vp, cm^3	17.24(0.43)	16.81(0.52)	0.43	-0.89 to 1.75	0.52
Δ % from the seated to supine posture					
OPJ (%)	8.94(3.12)	15.19(2.54)	-6.24	-14.16 to 1.67	0.12
CSA.mean (%)	7.79(2.09)	12.61(2.43)	-4.82	-11.12 to 1.48	0.13
Vp (%)	4.11(3.01)	11.56(3.29)	-7.44	-16.22 to 1.33	0.96

Abbreviations: OPJ = oropharyngeal junction, CSA.mean = mean pharyngeal cross-sectional area; Vp = pharyngeal volume; CI = confidence intervals. Data are presented as means $\pm$SEM.

Although the overall changes in UA calibre were not large, the fact that the comparisons with both a concurrent control group and repeated measurements in the same

individuals postpartum, and UA comparisons overall yielded similar findings increases confidence in the validity of the results.

Are the observed changes in UA size of clinical, or just physiological, significance? The changes that were reported in the results sections are at least as large as those found in comparisons between snorers and OSAHS patients (Martin et al 1995), men and women (Martin et al 1997). Furthermore the results are in keeping with the reported increase in snoring which is commoner in pregnancy and commonest in pre-eclampsia, thus to this extent at least it is likely that the changes in UA calibre are clinically significant.

Differences measured during wakefulness do not necessarily predict differences during sleep. The results reported in the thesis were obtained during wakefulness but during sleep the loss of UA defence by dilating muscle activity could result in further airway narrowing in the pregnant women. In fact in our studies snoring was reported more commonly by pregnant women than non-pregnant women. It is the audible indication of an increase in UA resistance. Edwards et al (2000b) have demonstrated a reversal of sleep-associated blood pressure increments in pre-eclampsia with the use of nocturnal nasal CPAP treatment, supporting the hypothesis that further UA obstruction occurs during sleeping. Thus, it is likely that narrowing of pharyngeal lumen during sleep may contribute to the increased rate of snoring and episodes of marked UAs resistance which is potentially associated with surges in blood pressure in an already compromised circulatory system. However, it has not been clarified whether changes in the UA contributes to snoring, increased UA resistance and blood pressure elevation.

From our results it is not possible to draw any firm conclusions about whether UA narrowing is a causative factor or simply a consequence of the development of pre-eclampsia; this is because of the study design (chapters 5 and 6). As mentioned earlier, a cross-sectional study cannot prove cause and effect, but can only suggest a cause if other known influences are controlled, as was the case in our studies (discussion sections of chapters 5 and 6). The longitudinal aspect of the study with repeated measurement post-partum supports the findings in the cross-sectional component. The mechanisms behind the UA narrowing in pregnancy and pre-eclampsia are not clear. Many reasons may cause UA narrowing and snoring in pregnancy including abdominal and neck loading, pharyngeal oedema of pregnancy and nasal congestion etc. Changes in BMI during pregnancy could account for the changes in pharyngeal area and we can speculate that the main reason for UA narrowing and snoring in pregnancy can be weight gain because total body fat leads to fat deposition, and differential local mass loading directly on the UA in pregnant women. The additional UA narrowing in pre-eclampsia is most likely due to tissue oedema in the neck and/or UA. This is compatible with the fact that most of the women with pre-eclampsia had significant peripheral oedema.

The findings from all the studies (chapter 5, 6 and 7) of this thesis confirmed that snoring occurs more frequently during pregnancy. In our studies, around twice as many pregnant women and even many more pre-eclamptic women snored compared to non-pregnant controls. In both the pre-eclamptic and healthy pregnant groups the rates of pre-pregnancy snoring were similar to those of the non-pregnant women. This suggests that the high rates of snoring in pre-eclampsia are acquired, not pre-morbid. It is likely

that the increasing prevalence of snoring are related to decreasing pharyngeal dimensions during pregnancy. However, reported breathing pauses were not as prevalent as snoring in pregnant and pre-eclamptic women in the face of UA narrowing. It is unlikely that severe apnoea develops in a woman who has never had OSAHS. However, to find out the percentage of pregnant women with UA narrowing who develop sleep apnoea or whether they will develop sleep apnoea requires further studies with recording of breathing during sleep. The findings of the studies in this thesis cannot clarify these issues due to the fact that we failed to perform sleep studies which is explained in chapter 8. Edwards et al (2000b) reported that in pre-eclamptic women, inspiratory flow limitation caused probably by UA narrowing was associated with a 10 to 20% decrease in tidal volume but this reduction did not produce apnoeas and measurable decreases in SaO_2.

UA narrowing and snoring occur commonly in normal pregnancy during sleep and improve after delivery. Pien et al (2005) reported that more than 10% of pregnant women may be at risk for developing sleep apnoea during pregnancy. In our prospective study with 50 women UA calibre increased and snoring decreased to pre-pregnancy levels after their delivery. Edwards et al (2005) demonstrated that both AHI and minimum overnight SaO_2 (in women who were diagnosed with sleep apnoea during late pregnancy) improve markedly after delivery. In contrast, Leung et al (2005) performed PSG on eight women with a normal pregnancy. There was no evidence of significant sleep-disordered breathing on PSG. However they did not have a non-pregnant control group to compare the finding regarding sleep related data. Also selection bias may have occurred due to the small number of the sample size. Furthermore, they used

thermisters to measure the respiratory airflow during PSG. This technique may underestimate the frequency of obstructive respiratory events. In addition, they did not measure oesophageal pressures during PSG. Thus it was possible that UARS might have been missed.

Excessive daytime sleepiness is common in pregnancy and becomes increasingly common as pregnancy progresses (Pien et al 2005). However, sleepiness in pregnant women is probably caused by factors other than the snoring or breathing pauses in the third trimester of pregnancy, according to our results in chapter 7. These factors can be comfort lying, backache, foetal movement, urinary frequency, uterine activity, general abdominal discomfort, leg cramps, restless legs syndrome and heartburn which are very common sleep disturbances in pregnancy (Driver and Shapiro 1992, Hertz et al 1992, Suzuki et al 1994, Edwards et al 2000a, AASM 2001, Hedman et al 2002, Lee et al 2004). Excessive daytime sleepiness is also associated with a wide variety of medical and mental conditions such as depression and fatigue, which may occur in pregnancy, in addition to sleep disturbances (Chervin 2000).

Additionally, an important implication of chapter 7 may be that although snoring and breathing pauses are more common in women with pre-eclampsia, they do not necessarily demonstrate more sleepiness, when compared with healthy pregnant women. This may be a very important clinical issue. That is, in the clinical setting, questions in regards to sleep-disordered breathing should extend beyond simply asking about sleepiness, but should instead focus on sleep-disordered breathing in women with pre-eclampsia.

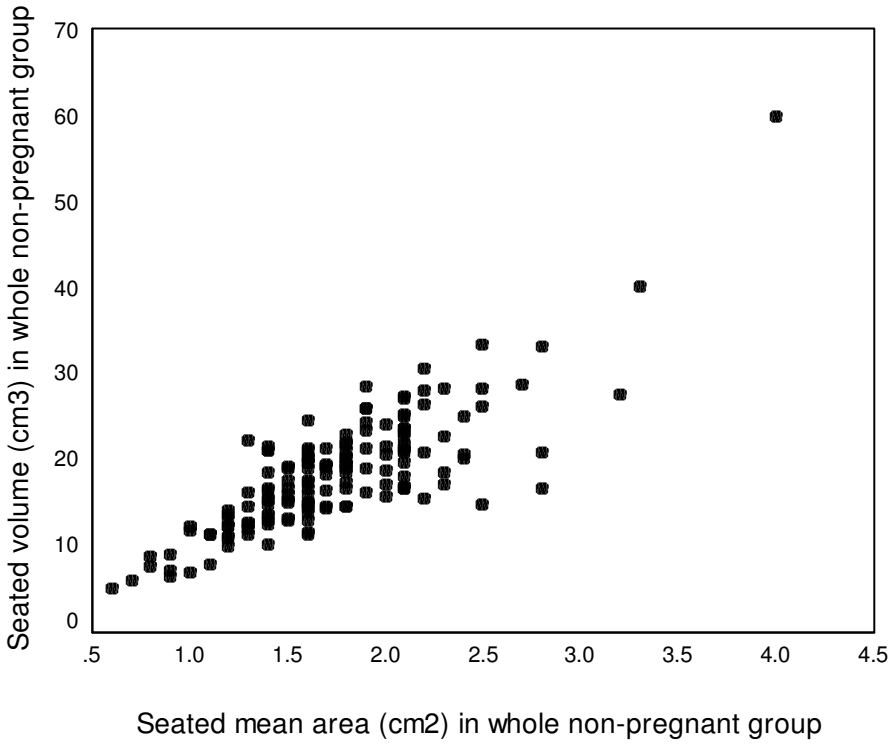
Systolic blood pressure in chapter 6 and 7 was higher in pregnant women when compared with non-pregnant women. Our conclusions on this have to be guarded as our blood pressures were based on single measurements in each case. Further the normal physiological response to pregnancy is a reduction in both systolic and diastolic blood pressure. When the healthy pregnant group was divided into snoring and non-snoring groups, snoring pregnant women's systolic and diastolic blood pressure were significantly higher than those of non-pregnant women (in chapter 7). However the validity of using a single casual blood pressure reading is questionable. Therefore in future studies, blood pressure measurements should be extended into the night (non-invasive 24-hour ambulatory blood pressure monitoring) to obtain more and better data and to assess whether the nocturnal blood pressure decrease occurs in the snorers.

In this thesis it would have been a more thorough approach to undertake studies with more objective results, such as results from PSG or MSLT. However, recruiting pregnant and especially pre-eclamptic women is associated with many difficulties, because pregnant women have many discomforts (urinary frequency, backache, leg cramps, etc). Additionally, the pre-eclamptic women are suffering from the onset of a serious illness. Further, our experiences with pre-eclamptic women (chapter 8) showed that even when they were recruited it is difficult to have them continue PSG recording for the whole night, given the many distractions (electrodes, cables, etc). So even if we did a study with PSG, it might not be as reliable as we might hope.

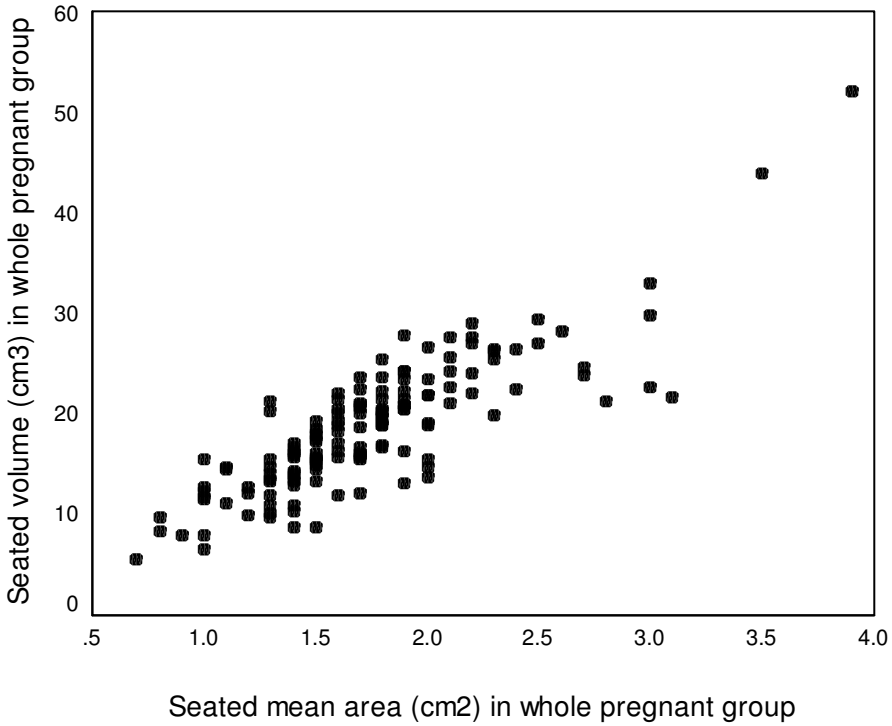
The reporting of sleep-related symptoms is problematic in these studies especially with features such as snoring. Both subjects and their partners were involved but some of them did not have a partner or their partner did not know if the woman snored. What is snoring to one partner may not be to another and subjects will only know if they snore if someone has objected. The potential for recall bias may also occur when pregnant females are asked around 3 months later about their pre-pregnancy snoring, breathing pauses, refreshment and sleepiness. Therefore, this part of the studies has significant limitations as do many or all questionnaire based studies. However, even if objective data were available regarding snoring from overnight PSG studies, it would be questionable to generalize this data to a cover period of 1 to 9 months with patients sleeping in their own homes.

Furthermore, in this thesis, we considered the possibility that the two measures used to indicate pharyngeal calibre (mean pharyngeal area and volume) could be linked by the use a common factor found in both measures, namely, mean pharyngeal area. It is expected that there is a linear relationship between these two measures. But when we look at the plots from our data (mean pharyngeal volume versus area) (figures X, 2 and 3) we see that there is variance in both as well. The mean area, however, seems to have less sources of variance than does the volume. A small change in distance is more likely to have a great statistical effect on volume than on mean area, even though physiologically it is unimportant. Therefore volume would seem to contribute additional variance, and not provide more information, than mean area. Thus, mean volume is not the preferred UA measurement.

Figure 9.1 (a) Pharyngeal volume versus mean area in non-pregnant women (n=150)



(b) Pharyngeal volume versus mean area in pregnant women (n=150)



In summary, the results of this thesis showed that UA calibre decreased significantly in healthy pregnant women, and particularly in pre-eclamptic women. OPJ and mean area are the preferred UA measurements. It is likely that decreased UA calibre may contribute to the increased rate of snoring and sleep-disordered breathing in pregnancy. Pregnant women were more sleepy but their sleepiness was not due to snoring or breathing pauses. In patients with pre-eclampsia, these UA changes could contribute to UA resistance episodes during sleep, which may further increase their blood pressure.

Future Studies

The clinical significance of the UA calibre changes requires further study. Perhaps UAs of women who intend to be pregnant before and during pregnancy can be measured. Pregnant women with UA narrowing can be compared with pregnant women without UA narrowing with respect to developing sleep-disordered breathing, pre-eclampsia or with intrauterine growth retardation. PSG could be used to measure further effects of UA narrowing in each trimester.

Clarification of the main reasons for UA narrowing and snoring in pregnancy, such as weight gain, will necessitate the use of different imaging techniques in order to determine whether this difference existed before pregnancy or occurred during pregnancy in a prospective study. For example, the relationship between indices of general obesity, BMI, neck circumference and percentage total body fat with neck fat deposition measured by MRI (after 12 weeks of pregnancy) or ultrasound could be examined in women before and during pregnancy (if possible after pregnancy) and

between women who develop pre-eclampsia and healthy pregnant women in the same study group.

It has not been determined whether UA narrowing develops due to pre-eclampsia-associated oedema or whether the presence of pre-pregnancy sleep-disordered breathing contributes to pre-eclampsia. Perhaps, women with sleep-disordered breathing who intent to be pregnant and a healthy non-pregnant group who intent to be pregnant can be followed during pregnancy. The prevalence of pre-eclampsia in each group can be compared.

Excessive daytime sleepiness is associated with daily fatigue, lack of energy, insomnia and depressed mood (Chervin 2000). When commencing a study related to snoring and excessive daytime sleepiness in pregnancy, these potential confounding variables should be controlled by excluding pregnant women with depression or other factor such as iron deficiency which can cause fatigue, lack of energy and other sleep disorders such as periodic leg movement etc.

Large prospective studies measuring the effect of pregnancy, in comparison to healthy controls, on sleep-disordered breathing are also lacking. Future studies are required to determine the true prevalence of sleep-disordered breathing in the pregnant population and its connection with pre-eclampsia and intrauterine growth retardation. There is also a need for randomised controlled trials of the effect of CPAP on sleep-disordered breathing and blood pressure in pre-eclampsia. Only if these studies show clear evidence of benefit from treating sleep-disordered breathing in pre-eclampsia, would wider

clinical detection of this issue be justified. If that were the case then conceivably patients could be evaluated at the first prenatal visit and subsequent visits for symptoms of sleep-disordered breathing, with the potential to diagnose, treat, and consequently reduce the possibility of associated pre-eclampsia, intrauterine growth retardation and lower Apgar scores at birth. Meanwhile any pregnant women with symptoms of sleep-disordered breathing should be considered for referral to a sleep clinic.

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APPENDICES

Appendix A: Pregnant women's informed consent form

SNORING IN PREGNANCY

We are asking for your help with a study to look at snoring in pregnancy. We will ask you, and your partner, to fill out a questionnaire about your sleep. Also we will ask you to do a short breathing test (5-10 minutes) in order to measure the size of your throat. You will breathe on a mouthpiece attached to a machine that sends sound-waves into your mouth.

We would like to repeat the same measurements on this same group of women 12 weeks after their pregnancies.

IT IS SAFE AND NEITHER YOU NOR YOUR BABY WILL BE EXPOSED TO ANYTHING HARMFUL.

Your assistance would be much appreciated, and would help us to guide the treatment of some of the problems which are associated with snoring in pregnant women such as high blood pressure and small for dates babies.

We will get in touch to arrange a mutually convenient time for the 10 minute test 12 weeks after your delivery. We realise that this may be difficult with your young family but believe this research is important to help future mothers and babies.

If you do not wish to do this, your treatment or care will not be affected in any way.

We greatly appreciate your help and assure you that any information you give us is strictly confidential, and will not be passed on to anyone else.

Many Thanks.

I ……..have read and understood the information above and agree to take part in this study.

Signed…… Date…….……

Signature of researcher…….. Date……..

Appendix B: Non-pregnant women's informed consent form

SNORING IN PREGNANCY

We are asking for your help with a study to look at snoring in pregnancy as a control person, i.e. someone who is not pregnant.

We will ask you, and your partner, to fill out a questionnaire about your sleep.

Also we will ask you to do a short breathing test (5-10 minutes) in order to measure the size of your throat.

You will breathe on a mouthpiece attached to a machine that sends sound-waves into your mouth.

IT IS SAFE AND YOU ARE NOT BEING EXPOSED TO ANYTHING HARMFUL.

We greatly appreciate your help and assure you that any information you give us is strictly confidential, and will not be passed on to anyone else.

Many Thanks.

I ……..have read and understood the information above and agree to take part in this study.

Signed…… Date……..……

Signature of researcher…….. Date…….

Appendix C: Sleep-Wake Questionnaire for Pregnant women

Name:…… Date of Birth:…….

Partner's Name:…… Date from completed:…….

SLEEP—WAKE QUESTIONNAIRE

Please fill out this questionnaire. Although some of the questions may seem personal all your answers will remain absolutely confidential. No information will be available to anyone other than the researcher you have spoken with.

If you have a partner, their questionnaire should be filled in by him without consulting you and returned to the Department of Sleep Medicine, NRIE in the stamped self-addressed envelope provided.

Many thanks for your help with this survey.

ABOUT YOU

Address:…… Tel No:……..
……..
……..
……..

Height:…….ft and inches/metres Weight:……stones/kg

Neck size…….
Waist size……...
Hip size……..

Do you have regular bed partner? Yes/ No

Occupation: current …… For…… years
Previous ……. For ……years

Do you perform shift- work or night work?
If so, please specify shift rotation pattern and how long you are on each shift

…… ..…….. ……...
…… ..…….. ……...
…… ..…….. ……...

Are you a : smoker / non-smoker / ex-smoker for …… years
Tobacco/Cigarettes use: …….number per day

Caffeinated and alcoholic drinks:
Tea cups per week …..…..
Coffee cups per week …..…....
Beer pints per week ……...
Wine glasses per week …….
Spirits drinks per week …….
Sherry/port glasses per week …….

Please list below all medications, including sleeping pills and inhalers, which you are currently taking

Name of medicine	**Dose**
1……	**……..**
2……	**……...**
3……	**..……..**
4……	**……...**
5……	**……...**

Have you ever had any of the following conditions or operations?
Please circle those applicable to you:

Asthma	*Hay fever*
High blood pressure	*Stroke*
Nasal congestion	*Nose operations*
Throat operations	*Diabetes*
Thyroid problems	*Epilepsy*
Broken nose	*Depression / Anxiety*
M.E./ Chronic fatigue syndrome	*Kidney / Liver problems*

Other Problems

Please circle any of the following events that you have ever experienced either in pregnancy or prior to becoming pregnant:

Hallucinations or vivid dreams whilst still conscious, occurring at sleep onset or on awakening

Paralysis or inability to move, occurring at sleep onset or on awakening

Muscular weakness or collapse whilst laughing or during strong emotions

Sensation of restlessness or crawling in legs, relived by standing or walking

Bed-wetting (as an adult)

Sleepwalking

EVENTS DURING SLEEP IN THE LAST MONTH

Please tick one column for each question to let us know about the presence and frequency of the following in THE LAST MONTH.

	Never	**Rare** (1-3 nights per month)	**Occasional** (1-2 nights per week)	**Often** (3-4 nights per week)	**Frequent or Always** (more than 4 nights per week)	**Don't know**
Snoring						
Breathing Pauses						

Snoring

If you snore, is the volume level: Quiet / Moderate / Heavy
(heard in bedroom only) (heard outside bedroom)

If you snore, is this: When on back only / On back and side / all positions

DAYTIME EVENTS IN THE LAST MONTH

How likely are you to doze of or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in THE LAST MONTH. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose ***the most appropriate number*** for each situation.

Scale

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high** chance of dozing

SITUATION	Chance of dozing (enter number below)
Sitting reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, when stopped for a few minutes in the traffic	

TOTAL ……..

(Please circle a number)

How refreshed do you feel on wakening in the morning regardless of sleep duration?

1	2	3	4	5

Unrefreshed **refreshed**

EVENTS DURING SLEEP PRIOR TO BECOMING PREGNANT

Please tick one column for each question to let us know about the presence and frequency of the following PRIOR TO BECOMING PREGNANT.

	Never	**Rare** (1-3 nights per month)	**Occasional** (1-2 nights per week)	**Often** (3-4 nights per week)	**Frequent or Always** (more than 4 nights per week)	**Don't know**
Snoring						
Breathing Pauses						

Snoring

If you snore, is the volume level: Quiet / Moderate / Heavy
(heard in bedroom only) (heard outside bedroom)

If you snore, is this: When on back only / On back and side / all positions

DAYTIME EVENTS PRIOR TO BECOMING PREGNANT

How likely were you to doze of or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life PRIOR TO BECOMING PREGNANT. Even if you did not do some of these things try to work out how they would have effected you. Use the following scale to choose ***the most appropriate number*** for each situation.

Scale

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high chance of dozing**

SITUATION	Chance of dozing (enter number below)
Sitting reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, when stopped for a few minutes in the traffic	

TOTAL ……..

(Please circle a number)

How refreshed do you feel on wakening in the morning regardless of sleep duration?

1	2	3	4	5

very unrefreshed **fully refreshed**

THANK YOU FOR YOUR HELP

Appendix D: Records of key medical history and baseline physical characteristics for pregnant women

RECORDS of KEY MEDICAL HISTORY and BASELINE PHYSICAL CHARACTERISTICS FOR PREGNANT WOMEN

DOS:

Name, Surname:

Do you have Asthma? Y / N

Do you get steroid treatment? Y / N

Did you suffer from sleep apnoea or other sleep disorders before/ during pregnancy?

Y/ N

……

……..……

NOB (number of baby): ( ) singleton ( ) multiple

DOB:

Gestational age:

EDD:

Height:

Current weight:

BMI:

Weight before pregnancy:

Pre-BMI:

Neck Size:

Waist Size:

Hip Size:

SBP:

DBP:

Sleeping Position: ( ) back ( ) front ( ) left ( ) right

COMMENTS:

Appendix E: The letter which was sent to women after their delivery at least 3 months later

Department of Sleep Medicine,
Royal Infirmary of Edinburgh,
51 Little France Cres.,
Little France
Edinburgh EH16 4SA

---- / ---- / 200-

Dear Ms……

When you were pregnant, you kindly helped us with a study into snoring and throat size in pregnant women. In this study we looked at women in the third trimester of their pregnancy, and tried to discover whether they had a narrower upper airway than their non-pregnant counterparts. We have obtained some significant findings from this, and would like to repeat the same measurements on this same group of women after their pregnancies. Therefore, we are writing to you to see if you are willing to help us. We would like to perform the same short breathing test on you which we did before, and ask you and your partner, if possible, to complete a similar questionnaire. Your assistance would be much appreciated, and would help us to guide the treatment of some of the problems which are associated with snoring in pregnant women such as high blood pressure and small-for-dates babies.

Please complete the enclosed form and return it in the enclosed stamped self-addressed envelope. We will then get in touch to arrange a mutually convenient time for the 10 minute test. We realise that this may be difficult with your young family but believe this research is important to help future mothers and babies. We will cover your travel expenses and child care costs if necessary. Could you and your partner please complete the enclosed questionnaires and bring them with you, when you come for your breathing test.

If you wish to receive further information, please contact us at one of the following phone numbers 0131-242 38 80, 242 38 79 or 242 38 82 (Research Fellow Bilgay Izci, Sister Marjorie Vennelle). A map has been enclosed of the New Royal Infirmary Hospital. On our meeting day, please come to the reception desk in area 3 (Gynea & Outpatient reception area).

Thank you very much for your help
Yours sincerely

NEIL J DOUGLAS, MD FRCP FRCPE
Professor of respiratory & Sleep Medicine

WANG A LISTON, MD FROG
Consultant in Obstetrics& Gynaecology

…….is / is not (delete as appropriate) able to help with this study. My telephone number is …….

Signed…….

Appendix F: Sleep-Wake Questionnaire for pregnant women's partner

Name:…… Date from completed:…….

Your Partner's Name:……

SLEEP-WAKE QUESTIONNAIRE FOR THE PARTNER

Please fill out this questionnaire about your partner's sleep. Although some of the questions may seem personal, all your answers will remain confidential. No information will be available to anyone other than the researcher you have spoken with.

It should be filled in independently by you without consulting your partner and returned to the Department of Sleep Medicine, NRIE in the stamped self-addressed envelope provided.

Many thanks for your help with this survey.

EVENTS DURING SLEEP IN THE LAST MONTH

Please tick one column for each question to let us know about the presence and frequency of the following for your partner in the LAST MONTH.

	Never	**Rare** (1-3 nights per month)	**Occasional** (1-2 nights per week)	**Often** (3-4 nights per week)	**Frequent or Always** (more than 4 nights per week)	**Don't know**
Snoring						
Breathing Pauses						

Snoring

If your partner snores, is the volume level: Quiet / Moderate / Heavy

(heard in bedroom only) (heard outside bedroom)

If your partner snores, is this: When on back only / On back and side / all positions

DAYTIME EVENTS IN THE LAST MONTH

How likely is your partner to doze of or fall asleep in the following situations, in contrast to feeling just tired? This refers to her usual way of life in THE LAST MONTH . Even if she has not done some of these things recently, try to work out how they would have effected her. Use the following scale to choose ***the most appropriate number*** for each situation.

Scale

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high** chance of dozing

SITUATION	Chance of dozing (enter number below)
Sitting reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, when stopped for a few minutes in the traffic	

TOTAL ……..

(Please circle a number)

EVENTS DURING SLEEP PRIOR TO YOUR PARTNER BECOMING PREGNANT

Please tick one column for each question to let us know about the presence and frequency of the following for your partner PRIOR TO BECOMING PREGNANT.

	Never	**Rare** (1-3 nights per month)	**Occasional** (1-2 nights per week)	**Often** (3-4 nights per week)	**Frequent or Always** (more than 4 nights per week)	**Don't know**
Snoring						
Breathing Pauses						

Snoring

If your partner used to snore, is the volume level: Quiet / Moderate / Heavy
(heard in bedroom only) (heard outside bedroom)

If your partner used to snore, is this: When on back only / On back and side / all positions

DAYTIME EVENTS PRIOR TO BECOMING PREGNANT

How likely was your partner to doze of or fall asleep in the following situations, in contrast to feeling just tired? This refers to her usual way of life PRIOR TO BECOMING PREGNANT. Even if she did not do some of these things try to work out how they would have effected her. Use the following scale to choose ***the most appropriate number*** for each situation.

Scale

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high** chance of dozing

SITUATION	Chance of dozing (enter number below)
Sitting reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, when stopped for a few minutes in the traffic	

TOTAL ……..

(Please circle a number)

THANK YOU FOR YOUR HELP

Appendix G: An advertisement for volunteers

VOLUNTEERS WANTED!

Could you spare 10-15 min. of your time to help with a medical research project?

We are carrying out a study on snoring in pregnancy and require non-pregnant female volunteers aged between 18 and 45 years to take part.

Study consists of a sleep questionnaire and a short breathing test which is non-invasive and no needles or any drugs are involved.

If you are not an enrolled student and interested in helping, please contact Bilgay Izci

Your help will be greatly appreciated!

For further info.

Tel: 0131-242 38 80, 242 38 79
E-mail: b.izci@ed.ac.uk

Appendix H: Sleep-Wake Questionnaire for non-pregnant women

Name:…… Date of Birth:……
Partner's Name:…… Date from completed:…….

SLEEP—WAKE QUESTIONNAIRE

Please fill out this questionnaire. Although some of the questions may seem personal all your answers will remain absolutely confidential. No information will be available to anyone other than the researcher you have spoken with.

If you have a partner, their questionnaire should be filled in by him without consulting you and returned to the Department of Sleep Medicine, NRIE in the stamped self-addressed envelope provided.

Many thanks for your help with this survey.

ABOUT YOU

Address:…… Tel No:……..
……..
……..
……..

Height:…….ft and inches/metres Weight:……stones/kg

Neck size…….
Waist size……...
Hip size……..

Do you have regular bed partner? Yes/ No

Occupation: current …… For…… years
Previous ……. For ……years

Do you perform shift- work or night work?
If so, please specify shift rotation pattern and how long you are on each shift

…… ..…….. ……...
…… ..…….. ……...
…… ..…….. ……...

Are you a : smoker / non-smoker / ex-smoker for …… years
Tobacco/Cigarettes use: …….number per day

Caffeinated and alcoholic drinks:
Tea cups per week ……..
Coffee cups per week …..…...
Beer pints per week ……...
Wine glasses per week …….
Spirits drinks per week …….
Sherry/port glasses per week …….

Please list below all medications, including sleeping pills and inhalers, which you are currently taking

Name of medicine	**Dose**
1……	……..
2……	……...
3……	..……..
4……	……...
5……	……...

Have you ever had any of the following conditions or operations?
Please circle those applicable to you:

Asthma	*Hay fever*
High blood pressure	*Stroke*
Nasal congestion	*Nose operations*
Throat operations	*Diabetes*
Thyroid problems	*Epilepsy*
Broken nose	*Depression / Anxiety*
M.E./ Chronic fatigue syndrome	*Kidney / Liver problems*

Other Problems

Please circle any of the following events that you have ever experienced:

Hallucinations or vivid dreams whilst still conscious, occurring at sleep onset or on awakening

Paralysis or inability to move, occurring at sleep onset or on awakening

Muscular weakness or collapse whilst laughing or during strong emotions

Sensation of restlessness or crawling in legs, relived by standing or walking

Bed-wetting (as an adult)

Sleepwalking

EVENTS DURING SLEEP IN THE LAST MONTH

Please tick one column for each question to let us know about the presence and frequency of the following in the last month.

	Never	**Rare** (1-3 nights per month)	**Occasional** (1-2 nights per week)	**Often** (3-4 nights per week)	**Frequent or Always** (more than 4 nights per week)	**Don't know**
Snoring						
Breathing Pauses						

Snoring

If you snore, is the volume level: Heav Quiet / Moderate / Heavy
(heard in bedroom only) (heard outside bedroom)

If you snore, is this: When on back only / On back and side / all positions

DAYTIME EVENTS IN THE LAST MONTH

How likely are you to doze of or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in THE LAST MONTH. Even if you have not done some of these things recently, try to work out how they would have effected you. Use the following scale to choose ***the most appropriate number*** for each situation.

Scale

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high** chance of dozing

SITUATION	Chance of dozing (enter number below)
Sitting reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, when stopped for a few minutes in the traffic	

TOTAL ……..

(Please circle a number)

How refreshed do you feel on wakening in the morning regardless of sleep duration?

1	2	3	4	5

Unrefreshed **refreshed**

THANK YOU FOR YOUR HELP

Appendix I: Sleep-Wake Questionnaire for non-pregnant women's partner

Name:…… Date from completed:…….

Your Partner's Name:……

SLEEP-WAKE QUESTIONNAIRE FOR THE PARTNER

Please fill out this questionnaire about your partner's sleep. Although some of the questions may seem personal, all your answers will remain confidential. No information will be available to anyone other than the researcher you have spoken with.

It should be filled in independently by you without consulting your partner and returned to the Department of Sleep Medicine, NRIE in the stamped self-addressed envelope provided.

Many thanks for your help with this survey.

EVENTS DURING SLEEP IN THE LAST MONTH

Please tick one column for each question to let us know about the presence and frequency of the following for your partner in the LAST MONTH.

	Never	**Rare** (1-3 nights per month)	**Occasional** (1-2 nights per week)	**Often** (3-4 nights per week)	**Frequent or Always** (more than 4 nights per week)	**Don't know**
Snoring						
Breathing Pauses						

Snoring

If your partner snores, is the volume level: Quiet / Moderate / Heavy
(heard in bedroom only) (heard outside bedroom)

If your partner snores, is this: When on back only / On back and side / all positions

DAYTIME EVENTS IN THE LAST MONTH

How likely is your partner to doze of or fall asleep in the following situations, in contrast to feeling just tired? This refers to her usual way of life in THE LAST MONTH. Even if she has not done some of these things recently, try to work out how they would have effected her. Use the following scale to choose ***the most appropriate number*** for each situation.

Scale

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high** chance of dozing

SITUATION	Chance of dozing (enter number below)
Sitting reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, when stopped for a few minutes in the traffic	

TOTAL ……..

(Please circle a number)

THANK YOU FOR YOUR HELP

Appendix J: Records of key medical history and baseline physical characteristics for non-pregnant women

RECORDS of KEY MEDICAL HISTORY and BASELINE PHYSICAL CHARACTERISTICS FOR NON-PREGNANT WOMEN

DOS:

Name, Surname:

Do you have Asthma? Y / N

Do you get steroid treatment? Y / N

Did you suffer from sleep apnoea or other sleep disorders? Y/ N

……..……

……

Height:

Current weight:

BMI:

Neck Size:

Waist Size:

Hip Size:

SBP:

DBP:

Sleeping Position: ( ) back ( ) front ( ) left ( ) right

COMMENTS:

Appendix K: Anthopometric variables and Upper airway measurements for subjects in chapter 5

Non-pregnant Women									%		
stead			supine			lateral			Changes from sit-sup		
OPJ	**CSA**	**Vp**	**OPJ**	**CSA**	**Vp**	**OPJ**	**CSA**	**Vp**	**OPJ**	**CSA**	**Vp**
1.3	1.5	15.3	1.5	.9	1.0	8.9	1.2	1.5	30.8	28.5	42.2
1.0	1.3	14.7	1.3	.9	1.5	14.5	1.2	2.1	10.0	-13.8	1.0
1.5	1.7	19.2	1.7	1.2	1.4	16.0	1.3	1.7	20.0	20.1	16.4
1.4	1.8	21.2	1.8	1.3	1.8	18.8	1.0	1.6	7.1	2.6	11.1
2.0	3.2	27.6	3.2	1.1	1.9	16.5	1.3	2.4	45.0	40.1	40.1
1.0	1.1	11.4	1.1	.6	.9	9.3	1.0	1.3	40.0	22.7	18.9
1.5	2.1	16.6	2.1	1.1	1.3	10.2	1.0	1.2	26.7	38.4	38.4
1.4	1.6	21.0	1.6	1.4	1.7	21.9	1.4	1.5	.0	-4.3	-4.3
1.8	2.1	16.9	2.1	1.5	1.8	19.4	1.5	1.9	16.7	16.7	-14.5
1.0	1.8	20.3	1.8	1.3	1.6	15.0	1.1	1.3	-30.0	10.6	26.1
2.4	2.1	23.1	2.1	1.8	1.7	16.7	1.7	1.9	25.0	20.5	27.8
1.8	2.3	28.3	2.3	1.1	1.3	15.1	.8	1.3	38.9	41.9	46.5
1.8	2.4	20.1	2.4	1.7	2.4	23.1	1.9	2.5	5.6	-2.8	-14.9
1.3	1.5	16.8	1.5	1.3	1.6	18.1	1.3	1.4	.0	-7.7	-7.7
.	.	.	.	.8	1.6	11.4	1.1	1.4	.	.	.
1.4	1.9	19.0	1.9	1.6	1.7	18.8	1.6	1.9	-14.3	10.0	1.1
1.1	1.8	21.8	1.8	1.3	1.7	19.1	1.3	1.9	-18.2	4.7	12.6
1.4	1.5	19.3	1.5	1.1	1.2	15.3	.9	1.2	21.4	20.7	20.7
1.9	1.9	24.3	1.9	1.0	1.8	19.1	1.2	1.5	47.4	2.9	21.6
.6	.9	6.5	.9	.8	1.1	12.0	1.4	1.8	-33.3	-23.5	-85.3
.7	.8	8.8	.8	.7	.9	9.8	.7	1.1	.0	-5.8	-10.8
1.9	2.3	22.7	2.3	1.7	2.0	19.5	1.9	2.0	10.5	13.9	13.9
1.4	1.7	14.6	1.7	1.1	1.5	15.4	1.4	1.6	21.4	14.3	-5.8
1.5	2.1	23.6	2.1	1.2	1.6	9.6	1.3	2.0	20.0	25.3	59.2
.7	1.3	22.2	1.3	.8	1.2	18.3	.7	1.4	-14.3	6.4	17.4
1.8	1.9	16.3	1.9	1.9	2.1	23.3	1.8	1.8	-5.6	-10.2	-42.6
1.3	2.2	30.7	2.2	1.5	1.7	24.1	1.5	1.5	-15.4	21.5	21.5
1.8	2.8	33.1	2.8	1.6	2.2	15.2	1.3	2.5	11.1	21.3	54.1
1.2	1.9	21.3	1.9	1.3	1.6	14.5	1.1	1.5	-8.3	17.1	32.2
1.3	1.6	12.9	1.6	1.1	1.7	18.7	1.5	1.5	15.4	-5.8	-45.5
1.3	1.6	19.7	1.6	1.3	1.6	19.5	1.5	1.3	.0	1.3	1.3
1.3	2.0	15.8	2.0	1.4	1.4	18.8	1.5	1.7	-7.7	26.5	-19.4
1.2	2.0	18.8	2.0	1.2	1.7	20.9	.9	1.5	.0	11.8	-11.5
1.0	1.9	26.0	1.9	.8	1.6	13.1	1.0	2.0	20.0	14.8	49.5
1.1	1.0	7.0	1.0	.9	.7	5.7	1.3	.	18.2	28.9	18.7
1.2	1.4	15.3	1.4	1.1	1.4	10.8	1.1	1.4	8.3	2.6	29.2
1.2	1.8	17.3	1.8	1.1	2.3	21.5	1.5	2.2	8.3	-24.3	-24.3
2.3	3.3	40.2	3.3	1.6	2.5	29.7	1.7	2.0	30.4	26.0	26.0
1.4	2.2	15.5	2.2	1.2	1.9	25.2	1.0	1.7	14.3	12.3	-62.8
1.5	2.8	20.9	2.8	1.7	2.1	25.3	1.9	2.4	-13.3	24.5	-20.8
1.6	2.1	25.3	2.1	1.2	1.7	18.2	1.4	1.9	25.0	18.0	28.3

1.3	1.8	18.5	1.8	.8	1.7	17.0	1.0	1.7	38.5	3.3	7.9
.9	2.0	21.5	2.0	1.1	2.1	16.4	1.0	2.1	-22.2	-4.9	23.7
1.5	2.1	27.1	2.1	1.6	1.7	21.7	1.4	2.0	-6.7	19.9	19.9
1.3	1.5	19.1	1.5	1.9	2.0	17.8	1.5	1.5	-46.2	-34.6	6.8
1.5	2.7	28.8	2.7	1.3	2.5	36.0	1.3	2.6	13.3	9.5	-25.0
1.0	2.2	20.9	2.2	1.4	2.4	24.0	1.3	2.4	-40.0	-9.1	-14.8
1.6	1.8	20.1	1.8	1.4	1.5	17.7	1.5	1.7	12.5	19.1	11.7
.9	1.4	16.5	1.4	.8	1.2	15.7	.9	1.7	11.1	18.9	4.8
1.4	2.1	21.7	2.1	.9	1.7	24.8	.9	1.8	35.7	17.2	-14.3
.8	1.9	25.9	1.9	.9	1.7	24.9	.8	2.1	-12.5	10.5	3.9
.9	1.3	12.1	1.3	.8	1.6	14.8	1.3	2.2	11.1	-16.0	-22.4
1.8	1.6	18.9	1.6	1.7	1.6	12.3	1.8	1.9	5.6	-4.0	35.0
1.2	1.7	19.3	1.7	.8	1.5	15.3	1.0	1.5	33.3	12.9	20.5
1.4	2.4	20.6	2.4	1.1	2.1	24.3	1.7	2.0	21.4	12.8	-18.0
.7	1.7	18.4	1.7	.6	1.2	12.1	.9	1.5	14.3	27.5	34.1
1.3	1.3	12.5	1.3	.9	1.3	9.3	1.3	1.7	30.8	-1.0	25.6
2.2	2.8	16.6	2.8	1.5	1.8	12.4	1.8	1.7	31.8	35.8	25.1
.9	1.6	17.6	1.6	.9	1.4	14.4	1.1	1.3	.0	10.3	18.5
1.6	2.5	28.2	2.5	.8	1.9	21.0	.8	.	50.0	22.1	25.5
1.3	2.1	27.4	2.1	1.1	1.6	21.3	.9	1.7	15.4	25.0	22.1
1.2	1.8	22.9	1.8	.9	1.4	12.9	.8	1.8	25.0	26.0	43.8
1.0	1.4	13.7	1.4	1.2	1.6	17.9	1.3	2.1	-20.0	-12.8	-30.7
.9	1.2	13.2	1.2	.9	1.4	11.8	1.0	1.5	.0	-15.2	11.0
1.7	2.3	18.5	2.3	1.3	1.8	14.6	1.2	1.7	23.5	21.1	21.1
1.0	1.2	10.9	1.2	1.0	1.9	13.0	1.2	1.6	.0	-53.5	-19.4
1.3	1.6	21.4	1.6	.9	1.7	24.0	1.2	1.7	30.8	-4.4	-12.1
1.7	2.2	26.5	2.2	1.4	1.8	22.4	1.7	2.4	17.6	18.9	15.5
3.7	4.0	59.7	4.0	2.0	3.4	30.6	1.9	2.7	45.9	14.6	48.7
1.1	1.3	16.2	1.3	1.1	1.1	16.6	1.4	1.4	.0	11.9	-2.2
1.3	1.4	15.6	1.4	1.2	1.3	14.7	1.2	1.5	7.7	5.5	5.5
.9	1.1	7.9	1.1	.6	.9	8.8	.9	.9	33.3	22.5	-10.8
2.1	1.6	15.1	1.6	.5	.	.	1.2	1.1	76.2	.	.
1.9	1.8	19.4	1.8	.8	1.3	16.0	1.0	1.5	57.9	27.6	17.8
.9	1.7	21.3	1.7	1.0	1.6	17.9	1.2	1.8	-11.1	4.5	16.0
1.3	1.8	19.4	1.8	.8	1.2	15.6	.9	1.3	38.5	34.5	19.6
.7	1.4	18.6	1.4	.4	.8	8.7	.5	1.0	42.9	45.1	53.2
1.3	1.4	14.9	1.4	.8	.	.	.7	.6	38.5	.	.
1.2	1.2	12.3	1.2	.8	1.1	12.5	.9	.9	33.3	7.6	-1.2
2.7	.	.	.	.8	1.3	10.5	.7	1.1	70.4	.	.
1.7	2.5	33.4	2.5	1.6	1.9	22.4	1.6	1.9	5.9	21.6	32.9
1.1	1.5	17.7	1.5	.8	1.3	18.6	1.0	1.4	27.3	13.3	-4.8
1.2	1.9	28.5	1.9	1.0	1.6	18.0	.8	1.8	16.7	17.8	37.0
1.4	1.6	14.8	1.6	1.2	2.0	18.2	1.8	2.5	14.3	-23.4	-23.4
1.4	1.8	14.5	1.8	1.0	1.5	16.0	1.3	1.9	28.6	19.7	-10.3
1.7	2.0	24.1	2.0	1.0	1.5	17.8	1.0	1.7	41.2	22.9	26.1
1.4	2.1	20.8	2.1	2.1	2.1	22.3	1.7	2.3	-50.0	-2.1	-7.2
1.9	2.1	21.4	2.1	1.4	1.7	23.8	1.5	1.6	26.3	20.4	-11.5

.9	1.8	22.1	1.8	.4	.	.	.7	2.0	55.6	.	.
1.1	1.6	24.6	1.6	1.3	1.6	23.6	1.2	1.9	-18.2	4.3	4.3
1.5	2.0	20.7	2.0	1.1	1.3	18.2	1.6	2.1	26.7	31.6	12.1
1.2	1.6	20.5	1.6	.9	.	.	1.1	1.8	25.0	.	.
1.7	1.4	21.0	1.4	1.4	1.2	16.1	1.4	1.4	17.6	17.5	23.2
1.8	1.8	16.6	1.8	1.6	1.8	19.3	1.6	1.8	11.1	4.6	-16.6
1.3	1.4	21.0	1.4	1.2	1.3	19.1	1.1	1.3	7.7	5.9	9.1
1.5	2.4	25.1	2.4	1.1	1.6	13.5	.8	1.6	26.7	33.4	46.1
1.8	2.2	28.1	2.2	.9	1.8	23.5	.6	1.6	50.0	16.5	16.5
.8	2.1	22.6	2.1	1.1	1.8	22.9	1.1	2.0	-37.5	14.1	-1.6
.4	.8	7.7	.8	1.4	2.0	19.0	.8	1.2	-250	-160	-146.8
2.3	2.1	21.1	2.1	1.3	1.5	15.4	1.9	2.0	43.5	27.0	27.0
Pregnant Women									**%**		
stead			**supine**			**lateral**			**Changes from sit-sup**		
OPJ	**CSA**	**Vp**	**OPJ**	**CSA**	**Vp**	**OPJ**	**CSA**	**Vp**	**OPJ**	**CSA**	**Vp**
1.0	1.5	15.4	1.5	.7	1.3	12.1	.9	1.6	30.0	8.3	21.4
1.3	1.3	20.3	1.3	.8	1.0	10.6	.9	1.3	38.5	22.7	47.7
1.4	2.0	23.5	2.0	1.4	1.2	13.4	1.2	1.1	.0	40.5	43.0
1.3	2.0	26.7	2.0	1.2	1.9	24.3	1.0	1.1	7.7	5.5	9.0
1.3	1.5	15.3	1.5	1.1	1.3	13.8	1.3	1.6	15.4	13.9	9.8
.9	1.1	11.2	1.1	.9	1.1	12.2	1.0	1.1	.0	1.0	-8.9
1.5	1.8	19.0	1.8	.9	1.7	26.2	1.3	2.1	40.0	6.6	-37.9
1.0	1.3	14.8	1.3	.9	1.1	11.7	1.1	1.4	10.0	21.3	21.3
1.5	2.6	28.3	2.6	1.1	1.8	16.6	.4	.7	26.7	28.4	41.4
1.7	2.0	21.8	2.0	1.6	1.8	18.1	2.1	1.9	5.9	8.5	16.8
1.0	1.8	16.8	1.8	1.1	1.6	20.6	1.0	1.8	-10.0	10.4	-22.6
.7	.	.	.	.8	1.8	17.2	1.1	1.7	-14.3	.	.
1.5	1.6	15.7	1.6	1.0	1.4	16.3	1.2	1.5	33.3	10.0	-3.5
.8	2.3	25.5	2.3	.9	1.7	18.3	.8	1.7	-12.5	28.3	28.3
1.4	1.4	13.6	1.4	1.1	1.1	15.4	1.3	1.4	21.4	20.3	-13.2
2.2	3.0	33.0	3.0	.9	1.8	20.8	1.6	1.9	59.1	39.6	36.9
1.6	2.3	26.3	2.3	1.3	1.6	17.1	1.4	1.7	18.8	29.0	35.2
1.0	1.6	12.0	1.6	.9	1.6	12.8	1.1	1.5	10.0	.0	-6.7
1.3	2.2	27.0	2.2	.7	1.7	14.9	1.0	2.4	46.2	23.5	44.9
1.5	1.8	22.2	1.8	1.3	1.5	12.8	1.4	1.7	13.3	15.2	42.3
1.4	1.4	15.6	1.4	1.1	1.7	21.9	1.2	1.7	21.4	-18.5	-40.1
1.0	1.8	18.8	1.8	1.2	1.8	22.9	1.4	1.7	-20.0	1.6	-21.8
1.5	1.9	20.8	1.9	1.0	1.6	16.8	1.3	2.1	33.3	15.4	19.3
1.3	1.9	20.5	1.9	.8	1.4	10.5	.9	1.9	38.5	25.2	49.0
1.2	1.5	14.9	1.5	.8	1.7	18.3	1.1	2.0	33.3	-11.7	-22.8
1.2	1.4	14.2	1.4	1.2	1.4	15.9	1.4	1.7	.0	-1.8	-12.0
1.4	1.9	22.3	1.9	1.3	1.7	21.7	1.7	1.9	7.1	10.3	2.5
1.3	1.6	18.3	1.6	.8	1.2	16.0	.8	1.3	38.5	25.8	12.8
.9	1.0	11.7	1.0	.8	1.0	14.1	.8	1.1	11.1	-2.9	-20.1
1.6	1.7	15.7	1.7	1.2	1.3	16.4	1.1	1.2	25.0	24.8	-4.5
1.0	1.0	11.6	1.0	1.0	1.0	13.3	.8	.9	.0	5.4	-15.2
1.6	2.1	27.6	2.1	1.5	1.7	16.9	1.3	1.4	6.3	20.3	38.7

1.0	.8	8.3	.8	2.2	2.4	27.6	1.4	1.4	-120	-205	-233.9
1.6	2.0	21.8	2.0	1.5	1.4	19.5	1.6	1.6	6.3	29.7	10.6
1.6	3.0	22.6	3.0	.8	1.6	17.1	.8	.	50.0	45.8	24.2
1.5	1.9	21.5	1.9	1.1	1.5	18.5	1.3	1.6	26.7	17.6	14.0
.4	.	.	.	.5	.8	4.3	.9	2.2	-25.0	.	.
1.3	1.8	20.5	1.8	1.1	1.4	13.7	1.1	1.4	15.4	23.4	33.4
1.4	1.9	24.2	1.9	.7	1.6	16.7	.9	1.9	50.0	14.4	30.8
2.4	3.1	21.6	3.1	.4	.	.	1.4	2.9	83.3	.	.
.9	1.4	10.3	1.4	1.4	1.8	18.7	1.6	1.6	-55.6	-30.0	-82.0
1.4	1.2	12.1	1.2	1.2	1.2	8.5	1.6	1.5	14.3	.2	30.2
1.3	2.1	21.1	2.1	1.0	1.7	18.1	1.4	1.7	23.1	18.1	14.0
2.2	1.9	27.9	1.9	1.1	1.3	14.2	1.0	1.5	50.0	32.8	49.0
1.7	2.0	14.8	2.0	1.4	1.7	20.0	1.7	2.6	17.6	15.5	-35.1
1.7	1.8	20.3	1.8	1.4	2.1	24.8	1.1	1.4	17.6	-12.3	-22.5
1.3	1.6	16.3	1.6	.9	1.5	14.6	1.0	1.4	30.8	10.7	10.7
1.6	1.5	16.1	1.5	1.1	1.4	15.9	.9	1.1	31.3	9.8	1.2
1.3	1.5	8.7	1.5	1.9	1.4	15.9	1.6	1.5	-46.2	.3	-82.8
1.0	.	.	.	1.1	1.8	20.3	1.4	2.0	-10.0	.	.
1.3	2.3	26.5	2.3	1.1	2.2	28.5	1.1	1.6	15.4	4.8	-7.6
1.0	2.4	22.4	2.4	1.0	.	.	1.1	2.2	.0	.	.
1.2	1.7	21.0	1.7	.8	1.3	10.6	1.3	2.0	33.3	24.1	49.4
1.2	1.7	20.8	1.7	1.0	1.6	18.4	.9	1.6	16.7	7.7	11.5
1.8	1.7	16.7	1.7	.	.	.	1.5	1.4	.	.	.
1.0	1.6	21.4	1.6	1.6	1.9	12.3	.	.	-60.0	-19.4	42.5
1.4	1.7	20.6	1.7	1.1	1.2	14.9	1.1	1.4	21.4	27.9	27.9
1.1	2.1	22.6	2.1	1.5	1.6	20.7	1.4	1.5	-36.4	25.9	8.2
1.2	1.5	14.6	1.5	.9	1.5	10.8	1.0	1.8	25.0	.1	26.4
1.2	1.9	24.2	1.9	1.0	1.5	17.4	.9	1.7	16.7	22.1	28.3
.8	1.4	17.1	1.4	.8	2.1	23.5	1.0	1.6	.0	-49.9	-37.4
.6	.	.	.	1.5	1.7	26.2	.8	1.3	-150	.	.
1.2	1.4	14.4	1.4	1.0	1.5	17.0	.9	1.3	16.7	-12.7	-18.1
1.0	1.3	15.4	1.3	1.0	1.3	13.3	1.0	1.3	.0	-3.6	13.6
1.0	1.8	16.7	1.8	.9	1.4	10.8	.8	2.0	10.0	17.8	35.1
1.2	1.6	20.5	1.6	1.2	1.3	14.8	1.4	1.8	.0	15.0	28.0
.6	1.0	12.4	1.0	.6	1.2	9.4	.5	1.0	.0	-22.5	24.6
1.7	2.1	24.3	2.1	1.1	1.7	16.8	1.4	1.6	35.3	20.6	30.9
1.2	1.8	19.9	1.8	1.2	1.8	10.8	1.5	2.2	.0	1.0	46.0
2.0	2.7	24.6	2.7	1.6	2.2	21.4	2.1	2.4	20.0	17.6	13.0
1.8	2.0	18.9	2.0	1.6	1.6	20.5	1.5	1.8	11.1	20.9	-8.2
1.5	1.7	15.8	1.7	1.3	1.7	16.8	1.5	1.8	13.3	-1.3	-6.7
.4	1.0	12.7	1.0	.8	2.0	20.8	.8	2.2	-100.0	-94.5	-63.4
1.6	1.8	19.6	1.8	.9	1.2	16.1	1.3	1.4	43.8	33.1	17.9
1.0	1.7	18.7	1.7	.7	1.6	14.8	1.0	1.8	30.0	3.3	20.9
.6	.8	9.8	.8	.9	.9	10.2	.7	.9	-50.0	-.3	-4.6
1.1	1.8	23.6	1.8	1.0	.	.	1.3	1.4	9.1	.	.

1.2	1.3	13.3	1.3	.9	1.4	12.4	.8	1.2	25.0	-3.2	7.1
1.1	2.0	19.0	2.0	1.1	1.2	6.7	1.2	1.6	.0	39.1	64.7
1.1	1.4	16.1	1.4	1.2	1.5	20.8	1.0	1.8	-9.1	-6.1	-29.2
1.3	1.7	23.6	1.7	1.4	1.6	12.6	1.4	2.2	-7.7	10.3	46.8
1.6	2.5	29.4	2.5	1.6	1.6	14.8	1.4	1.3	.0	36.4	49.7
1.4	1.4	16.6	1.4	1.0	1.3	12.8	1.4	1.4	28.6	6.7	23.0
.7	1.3	21.3	1.3	.7	1.1	17.2	.7	1.3	.0	11.2	19.2
.8	.9	7.9	.9	1.0	1.2	10.6	1.1	1.0	-25.0	-26.9	-34.4
1.0	1.0	8.0	1.0	.5	.	.	.5	.9	50.0	.	.
1.2	1.5	15.3	1.5	1.0	1.2	11.2	1.0	1.3	16.7	18.8	26.9
1.3	1.4	8.8	1.4	1.0	1.5	13.9	1.3	1.3	23.1	-8.1	-58.0
1.2	1.5	17.8	1.5	.9	1.6	25.9	1.4	1.5	25.0	-4.4	-45.2
.8	1.1	14.8	1.1	.5	1.0	9.4	.6	1.2	37.5	6.9	36.8
1.7	1.5	18.1	1.5	1.1	1.4	13.8	1.2	1.4	35.3	8.8	24.0
1.7	1.7	22.5	1.7	1.2	1.4	15.3	1.3	1.5	29.4	16.8	32.2
1.9	2.2	24.0	2.2	.9	1.9	19.7	1.2	1.9	52.6	14.2	18.1
.9	1.0	15.5	1.0	.9	1.4	20.1	1.1	1.4	.0	-38.9	-29.7
1.5	1.4	13.4	1.4	1.2	1.6	15.7	1.2	1.5	20.0	-17.2	-17.2
.9	1.1	14.6	1.1	.7	.8	8.4	1.0	.9	22.2	29.2	42.8
1.2	2.2	29.1	2.2	1.2	1.6	13.4	1.3	1.3	.0	29.7	54.0
1.3	1.9	20.4	1.9	1.3	1.8	24.9	1.4	1.7	.0	8.6	-21.8
.9	1.4	16.3	1.4	.9	1.3	17.6	1.5	1.4	.0	11.3	-8.0
1.2	1.9	23.4	1.9	1.4	1.8	24.0	1.1	2.2	-16.7	5.1	-2.8

Appendix L: Anthopometric variables and ESS score for subjects in chapter 7

Non-Pregnant												
Age	**Height**	**Pre Weight**	**Pre BMI**	**NC**	**SBP**	**DBP**	**Women**		**Pre Refresh**	**Preg Refresh**	**Partner**	
							Preg ESS	**Pre ESS**			**Preg ESS**	**Pre ESS**
27	1.75	80	26	34	108	71	3	3	4	4	.	.
25	1.72	59	20	30	93	61	3	3	5	5	4	4
24	1.66	71	26	34	104	86	5	5	4	4	5	5
36	1.63	58	22	32	89	63	4	4	4	4	5	5
22	1.67	69	25	33	97	68	7	7	3	3	2	2
21	1.63	72	27	33	95	74	1	1	4	4	.	.
18	1.67	85	30	32	103	83	6	6	3	3	.	.
19	1.63	57	21	33	106	79	9	9	2	2	.	.
31	1.71	76	26	33	100	70	3	3	2	2	.	.
33	1.82	80	24	35	100	60	1	1	4	4	.	.
31	1.59	57	23	32	105	60	3	3	2	2	.	.
20	1.59	59	23	33	102	66	5	5	4	4	.	.
23	1.70	67	23	34	119	79	4	4	4	4	.	.
29	1.59	70	28	33	90	70	15	15	2	2	.	.
29	1.63	64	24	32	90	60	9	9	2	2	.	.
36	1.60	57	22	33	85	65	4	4	4	4	2	2
29	1.60	64	25	34	90	60	3	3	2	2	2	2
25	1.63	48	18	31	101	72	7	7	3	3	.	.
32	1.62	55	21	32	113	74	2	2	5	5	1	1
40	1.50	51	23	31	105	62	7	7	2	2	9	9
40	1.68	76	27	37	117	66	13	13	2	2	10	10
29	1.49	54	24	32	82	59	6	6	2	2	.	.
25	1.70	65	22	32	98	69	.	.	.	.	.	.
28	1.51	75	33	31	103	67	.	.	.	.	.	.
27	1.64	66	24	34	113	58	2	2	4	4	.	.
41	1.57	57	23	32	122	88	5	5	3	3	5	5
31	1.65	64	23	31	123	78	.	.	.	.	.	.
36	1.60	96	38	39	120	80	5	5	3	3	6	6
27	1.61	60	23	34	119	74	3	3	3	3	5	5
26	1.56	56	23	32	110	65	7	7	3	3	.	.
26	1.62	64	25	34	121	99	9	9	3	3	.	.
38	1.60	64	25	34	135	79	1	1	3	3	1	1
38	1.50	58	26	33	108	73	.	.	.	.	.	.
29	1.57	57	23	33	113	67	.	.	.	.	.	.
40	1.68	64	23	33	129	79	16	16	1	1	12	12
30	1.70	64	22	31	126	79	2	2	3	3	.	.
25	1.64	56	21	32	97	60	5	5	3	3	.	.
21	1.68	67	24	32	92	63	11	11	4	4	.	.
20	1.61	76	29	34	95	67	15	15	5	5	.	.
36	1.72	64	22	34	114	72	2	2	5	5	6	6

28	1.69	63	22	31	105	70	5	5	2	2	.	.
31	1.60	53	21	33	109	67	3	3	3	3	3	3
39	1.62	60	23	33	90	58	5	5	4	4	2	2
29	1.67	57	20	33	119	81	11	11	2	2	.	.
40	1.55	54	22	31	124	83	6	6	5	5	3	3
23	1.63	65	24	36	125	73	5	5	2	2	.	.
30	1.57	51	21	31	110	85	6	6	3	3	7	7
34	1.67	69	25	34	121	83	10	10	4	4	17	17
25	1.65	67	25	33	120	78	3	3	3	3	.	.
30	1.57	56	23	33	93	67	3	3	4	4	4	4
40	1.58	67	27	36	127	65	6	6	3	3	.	.
42	1.65	60	22	32	105	79	3	3	2	2	.	.
26	1.65	54	20	31	120	70	5	5	4	4	.	.
42	1.70	79	27	34	138	69	0	0	3	3	.	.
45	1.50	47	21	31	129	79	4	4	4	4	.	.
26	1.76	64	20	33	128	74	3	3	2	2	.	.
39	1.60	75	29	33	104	62	4	4	4	4	4	4
37	1.76	64	21	31	100	70	1	1	5	5	1	1
31	1.58	58	23	31	.	.	.	.	.	.	.	.
26	1.68	.	.	29	100	70	5	5	4	4	8	8
27	1.63	60	23	32	.	.	3	3	4	4	1	1
21	1.74	53	18	32	115	77	2	2	4	4	3	3
31	1.78	64	20	30	122	83	6	6	3	3	.	.
31	1.59	45	18	30	99	77	5	5	.	.	6	6
40	1.69	62	22	32	103	68	11	11	4	4	8	8
37	1.70	95	33	36	94	66	4	4	2	2	3	3
36	1.66	61	22	33	105	72	7	7	4	4	.	.
29	1.68	52	19	30	103	67	7	7	3	3	.	.
27	1.65	68	25	32	107	69	6	6	3	3	0	0
42	1.68	83	29	36	109	73	7	7	2	2	2	2
27	1.70	56	19	31	117	72	3	3	4	4	4	4
28	1.58	95	38	36	114	81	4	4	3	3	3	3
24	1.78	70	22	34	128	68	4	4	3	3	.	.
27	1.63	85	32	36	136	83	9	9	3	3	.	.
34	1.58	54	22	31	121	71	7	7	4	4	18	18
42	1.60	67	26	32	114	77	3	3	.	.	.	.
43	1.70	67	23	32	114	74	0	0	4	4	6	6
25	1.63	60	23	32	110	67	9	9	3	3	.	.
42	1.53	61	26	33	90	70	.	.	.	.	.	.
33	1.63	89	34	39	106	70	3	3	3	3	5	5
35	1.50	52	23	28	105	69	9	9	4	4	7	7
23	1.73	67	22	32	107	58	9	9	3	3	.	.
28	1.75	64	21	32	103	66	4	4	2	2	4	4
23	1.65	64	23	33	103	65	3	3	2	2	.	.
34	1.61	79	31	33	111	72	1	1	2	2	.	.
25	1.61	71	27	33	110	79	13	13	3	3	.	.
37	1.50	56	25	32	91	64	9	9	3	3	11	11

30	1.63	55	21	33	90	68	4	4	2	2	.	.
26	1.58	96	39	32	105	55	4	4	3	3	.	.
38	1.63	55	21	32	114	68	2	2	3	3	.	.
38	1.68	55	19	31	95	65	8	8	2	2	13	13
42	1.60	60	23	31	90	70	3	3	4	4	2	2
37	1.50	53	23	30	110	70	11	11	2	2	4	4
24	1.66	70	25	32	80	50	1	1	1	1	.	.
37	1.58	59	24	34	90	50	5	5	4	4	.	.
26	1.63	62	23	31	80	60	.	.	.	.	.	.
44	1.60	63	25	30	90	55	4	4	2	2	3	3
43	1.73	62	21	32	110	70	9	9	3	3	8	8
29	1.55	76	32	33	113	70	8	8	2	2	.	.
23	1.60	51	20	31	100	65	5	5	3	3	.	.
33	1.65	85	31	33	138	94	8	8	3	3	.	.
22	1.69	60	21	32	110	70	9	9	2	2	6	6
21	1.68	64	23	34	95	75	3	3	2	2	.	.
24	1.73	63	21	33	100	70	8	8	2	2	12	12
23	1.65	70	26	34	130	100	6	6	4	4	.	.
36	1.63	75	28	35	100	80	3	3	3	3	0	0
28	1.70	63	22	31	110	80	7	7	2	2	10	10
32	1.64	63	23	32	100	70	4	4	3	3	5	5
38	1.70	73	25	35	110	80	.	.	.	.	.	.
28	1.64	59	22	32	90	65	6	6	4	4	6	6
37	1.55	55	23	32	100	90	3	3	2	2	3	3
24	1.70	57	20	32	106	60	0	0	3	3	.	.
25	1.67	95	34	37	140	69	5	5	2	2	3	3
31	1.60	57	22	32	114	64	2	2	4	4	.	.
27	1.60	56	22	30	106	57	.	.	.	.	.	.
34	1.63	68	26	35	.	.	11	11	4	4	12	12
23	1.55	53	22	32	114	79	.	.	.	.	3	3
37	1.59	76	30	35	90	70	3	3	2	2	3	3
34	1.72	64	22	34	88	53	15	15	2	2	14	14
40	1.68	82	29	35	100	80	8	8	3	3	4	4
36	1.65	73	27	35	112	63	.	.	.	.	.	.
38	1.60	95	37	40	100	60	1	1	3	3	8	8
32	1.55	60	25	34	100	70	1	1	4	4	.	.
25	1.58	70	28	35	115	85	1	1	4	4	0	0
37	1.68	59	21	32	107	63	5	5	3	3	.	.
31	1.61	65	25	33	144	92	3	3	4	4	.	.
25	1.68	61	22	34	103	71	7	7	2	2	.	.
37	1.58	73	29	38	141	87	4	4	3	3	7	7
40	1.60	60	23	32	114	71	8	8	2	2	.	.
30	1.68	64	23	32	98	63	2	2	3	3	0	0
32	1.68	76	27	36	116	75	7	7	3	3	5	5
32	1.69	64	22	33	106	67	5	5	3	3	14	14
24	1.61	51	20	31	116	75	5	5	3	3	.	.
45	1.68	60	21	32	110	70	8	8	3	3	.	.

40	1.64	65	24	34	100	70	4	4	3	3	5	5
35	1.58	59	24	34	125	100	6	6	1	1	.	.
43	1.60	53	21	31	90	70	4	4	4	4	.	.
34	1.63	60	23	32	117	81	3	3	4	4	.	.
33	1.70	89	31	37	130	81	4	4	2	2	2	2
41	1.63	54	20	33	111	71	6	6	2	2	.	.
33	1.65	83	30	32	123	81	8	8	2	2	12	12
26	1.68	.	.	34	127	73	15	15	3	3	11	11
27	1.63	48	18	30	110	75	11	11	2	2	.	.
40	1.62	60	23	31	110	70	2	2	2	2	.	.
26	1.63	.	.	36	83	60	11	11	3	3	5	5
27	1.58	.	.	37	138	103	5	5	3	3	.	.
45	1.65	70	26	34	85	45	2	2	5	5	0	0
39	1.70	72	25	32	100	80	4	4	2	2	4	4
39	1.55	73	30	32	110	80	6	6	2	2	.	.
22	1.80	76	23	36	95	70	5	5	4	4	.	.
26	1.58	68	27	36	120	66	5	5	3	3	.	.
19	1.63	79	30	36	110	72	6	6	4	4	.	.
22	1.70	64	22	33	.	.	13	13	1	1	8	8
36	1.63	57	22	33	90	70	.	.	.	.	.	.
28	1.55	49	20	30	80	60	5	5	1	1	.	.
28	1.68	92	33	38	100	80	6	6	2	2	0	0
29	1.64	60	22	33	110	70	3	3	4	4	.	.
35	.	.	.	.	.	.	12	12	3	3	12	12
26	.	.	.	.	.	.	11	11	2	2	11	11
29	.	.	.	.	.	.	11	11	1	1	11	11

Pregnant

Age	Height	Pre Weight	Pre BMI	NC	SBP	DBP	Women		Pre Refresh	Preg Refresh	Partner	
							Preg ESS	Pre ESS			Preg ESS	Pre ESS
32	1.66	64	23	34	120	79	7	7	3	3	7	7
17	.	.	.	34	110	60	7	4	3	3	.	.
28	1.67	56	20	.	110	55	17	6	2	4	5	5
19	.	64	.	32	.	.	20	11	1	4	19	9
19	1.62	51	19	31	120	70	3	3	1	1	0	0
16	.	.	.	32	.	.	8	8	2	2	.	.
30	.	60	.	33	110	60	11	5	2	3	10	7
32	1.56	60	24	32	120	85	3	1	3	3	7	3
35	.	.	.	34	150	88	14	3	1	2	10	3
27	1.64	53	20	31	110	65	9	3	4	5	12	4
37	1.63	64	24	33	130	70	2	1	3	4	2	3
37	1.63	57	22	34	130	78	6	0	3	5	8	2
34	1.57	57	23	35	124	80	12	7	2	4	9	11
25	1.65	.	.	34	122	70	1	0	4	4	0	0
18	1.52	.	.	32	121	58	7	1	1	3	.	.
32	1.58	52	21	35	120	70	10	8	4	4	4	3
17	1.66	.	.	36	120	78	0	0	2	4	0	0

29	1.63	49	18	31	110	66	5	5	3	4	6	3
30	1.75	67	22	32	120	75	9	.	4	.	5	5
28	1.58	52	21	31	100	68	6	1	2	3	5	1
29	1.60	51	20	31	118	71	14	8	2	4	11	5
37	1.65	73	27	34	110	70	12	11	4	4	.	.
20	1.70	54	19	33	110	70	19	6	1	3	.	.
30	1.63	65	24	32	106	66	3	1	3	4	7	1
32	1.57	57	23	33	140	88	0	0	4	5	9	3
32	1.68	83	29	36	.	.	4	7	4	.	3	3
29	1.73	76	25	37	120	80	.	3	.	5	.	.
40	1.60	58	23	34	100	70	5	2	3	5	7	2
33	1.70	61	21	32	110	70	10	5	3	2	14	13
30	1.69	59	21	34	110	65	10	6	2	.	11	7
32	1.65	67	24	35	110	70	2	0	3	4	1	0
36	1.69	70	24	33	120	88	12	3	3	4	7	4
28	1.68	119	42	40	138	76	6	9	4	4	11	7
26	1.62	110	42	37	140	78	.	.	.	.	.	.
37	1.64	74	27	36	144	90	.	.	.	.	.	.
32	1.68	60	21	34	104	64	4	4	4	4	2	4
45	1.68	60	21	31	100	60	.	4	.	2	.	.
33	1.77	60	19	32	110	60	12	4	2	4	5	4
36	1.55	51	21	31	95	57	.	.	.	.	.	.
38	1.68	76	27	35	150	88	10	5	2	3	.	.
38	1.63	48	18	32	110	78	9	2	3	5	.	.
32	1.62	64	24	33	110	70	.	5	.	3	.	.
35	1.74	65	21	35	117	78	9	7	3	4	14	7
33	1.68	61	22	34	120	75	11	8	4	4	.	.
28	1.54	64	27	34	120	70	9	0	2	4	7	1
34	1.80	90	28	38	120	68	10	2	3	4	11	4
26	1.80	86	26	36	130	80	7	9	3	2	7	6
35	1.62	88	34	36	128	84	10	4	3	5	4	3
33	1.63	56	21	33	117	90	.	.	.	.	.	.
39	1.72	63	21	34	118	68	10	5	2	3	4	2
32	1.60	76	30	34	120	75	1	0	1	3	4	1
31	1.60	86	33	35	128	72	.	.	.	.	.	.
32	1.58	45	18	32	120	80	2	2	3	3	2	2
35	1.59	54	21	34	120	70	7	6	3	3	7	7
31	1.57	49	20	31	106	71	12	8	2	2	5	4
34	1.58	54	22	33	114	70	9	2	3	4	10	8
25	1.52	55	24	32	100	69	6	6	2	4	8	8
35	1.78	67	21	33	110	70	3	0	2	5	.	.
41	1.68	.	.	34	121	59	10	3	4	5	9	3
36	1.58	86	35	34	110	70	9	3	5	5	6	4
33	1.63	57	22	32	127	65	5	4	4	2	4	4
29	1.55	48	20	31	122	76	6	1	3	3	.	.
25	1.53	54	23	35	127	70	.	.	5	5	.	.
37	1.63	48	18	32	90	60	4	0	3	5	12	12

31	1.68	67	24	33	133	91	2	0	2	4	.	.
37	1.78	70	22	34	130	84	2	0	4	4	5	4
22	1.63	52	20	31	107	59	3	3	3	4	.	.
35	1.55	54	22	31	90	70	5	3	4	4	8	5
27	1.58	79	32	36	117	61	9	3	2	3	.	.
39	1.60	64	25	34	100	70	5	3	3	5	9	4
33	1.59	52	21	32	103	72	7	4	2	3	5	5
29	1.58	57	23	34	126	76	15	.	2	.	8	4
20	1.55	45	19	31	90	50	12	14	1	1	5	5
35	1.70	60	21	32	110	70	3	3	3	3	5	4
.	1.58	50	20	32	110	80	.	.	.	.	.	.
18	1.83	53	16	32	95	75	7	4	3	2	5	4
37	1.53	49	21	30	120	80	7	2	3	5	8	8
32	1.68	86	30	36	142	78	.	.	.	.	.	.
?	1.58	60	24	?	120	72	?	5	?	4	9	4
37	1.63	72	27	35	108	72	13	5	3	4	.	.
21	1.75	70	23	35	124	77	2	0	2	4	.	.
36	1.61	64	24	32	113	75	9	4	3	4	12	7
31	1.68	54	19	31	110	70	8	8	4	3	7	5
27	1.70	90	31	37	105	70	.	.	.	.	.	.
40	1.68	59	21	32	130	85	11	6	4	5	7	3
33	1.75	65	21	37	110	85	9	7	4	3	14	11
24	1.58	53	21	29	110	60	4	4	3	3	5	4
28	1.70	60	21	33	130	84	13	11	2	3	10	12
24	1.58	73	29	36	105	90	2	.	3	.	.	.
30	1.73	60	20	34	100	75	10	4	4	5	14	7
26	1.60	54	21	.	100	56	3	3	3	3	.	.
24	1.63	70	26	33	110	70	9	3	2	3	.	.
42	1.63	.	.	.	126	84	6	6	2	3	8	3
36	1.58	67	27	37	130	80	14	10	3	5	.	.
33	1.70	79	27	36	100	80	12	8	2	4	3	3
31	1.68	92	33	35	137	73	3	0	4	5	2	1
28	1.53	48	20	29	120	90	7	4	3	4	5	9
32	1.71	64	22	32	129	68	1	0	3	3	4	.
38	1.70	76	26	.	115	79	3	5	3	5	5	4
19	1.53	73	31	34	.	.	7	5	3	4	9	3
26	1.73	70	23	38	.	.	16	14	1	1	.	.
22	1.71	67	23	35	.	.	9	6	3	2	9	9
27	1.68	51	18	33	.	.	3	3	2	3	1	1
20	1.70	48	16	31	110	70	4	3	3	3	.	.
36	1.65	67	24	34	130	80	7	2	2	4	8	3
38	1.65	76	28	32	110	83	1	1	2	3	0	0
29	1.63	67	25	33	110	80	4	3	3	4	.	.
19	1.65	48	17	31	100	92	8	2	2	3	.	.
19	1.61	60	23	32	100	80	9	3	3	4	6	3
20	1.53	48	20	33	114	72	19	.	.	.	.	.
34	1.70	67	23	34	129	106	13	7	3	4	.	.

34	1.60	54	21	33	.	.	11	10	2	4	5	5
33	1.65	.	.	32	120	80	.	.	.	.	0	0
37	1.68	73	26	33	130	70	5	4	3	3	.	.
30	1.70	83	28	36	130	90	4	3	3	3	.	.
36	1.60	54	21	32	98	60	1	1	2	4	8	3
24	1.65	54	20	30	128	55	9	11	4	4	.	.
34	1.63	68	26	35	130	70	9	6	3	5	7	4
22	1.58	48	19	31	115	68	13	10	2	3	.	.
27	1.60	64	25	35	115	70	3	4	3	4	3	3
31	1.65	79	29	38	120	85	11	5	1	3	.	.
29	1.58	67	27	34	110	80	4	2	2	2	7	5
36	1.70	64	22	35	110	68	4	3	3	4	5	2
36	1.55	58	24	34	.	.	2	0	2	3	8	13
27	1.58	67	27	32	120	80	11	6	2	4	6	4
32	1.70	67	23	32	120	95	6	4	4	5	4	5
27	1.77	60	19	34	100	70	12	5	3	4	7	4
22	1.71	70	24	35	110	70	14	5	5	5	9	3
33	1.70	70	24	36	110	90	.	.	.	.	.	.
25	1.70	57	20	32	110	60	12	7	3	4	13	4
37	1.70	57	20	32	110	70	10	2	3	4	14	4
29	1.63	100	38	37	138	63	8	4	3	4	11	5
19	1.58	59	24	31	90	67	5	5	3	3	.	.
32	1.60	57	22	32	120	90	6	2	2	5	6	2
27	1.68	64	23	36	110	80	11	5	1	3	13	4
32	1.55	86	36	36	121	72	6	2	2	4	7	3
24	1.70	.	.	36	127	75	10	11	2	2	6	14
.	1.71	87	30	32	.	.	.	.	.	.	.	.
26	1.65	61	22	?	100	60	?	2	?	?	.	.
23	1.65	57	21	35	110	65	2	0	4	?	4	2
34	1.56	64	26	32	96	58	1	0	2	3	.	.
35	1.83	70	21	34	140	75	10	5	3	5	9	7
32	1.60	51	20	33	120	88	.	5	.	3	0	0
35	1.68	63	22	35	110	71	10	7	3	5	.	.
30	1.68	67	24	33	113	58	5	5	2	3	12	9
33	1.70	67	23	35	120	65	.	.	.	.	.	.
33	1.70	61	21	32	130	75	8	3	3	5	.	.
29	1.68	70	25	32	120	70	12	7	4	4	9	7
35	1.65	79	29	39	139	100	2	0	3	4	.	.
31	1.53	54	23	34	120	60	9	9	4	4	5	5
29	1.60	.	.	.	116	70	0	4	3	2	.	4
21	1.75	79	26	37	127	82	3	8	4	3	8	8
39	1.68	73	26	34	120	80	3	3	1	3	.	.
23	1.61	51	20	34	.	.	14	5	3	2	6	8
20	1.61	60	23	33	.	.	.	.	.	.	.	.
27	1.63	54	20	30	83	50	8	4	3	2	5	4
37	1.70	60	21	33	110	80	.	.	.	.	.	.
35	1.70	.	.	.	120	80	5	3	4	5	5	5

28	1.73	67	22	35	104	60	.	.	.	.	3	1
33	1.63	75	28	34	99	65	11	6	2	3	9	2
23	1.62	54	21	.	120	60	3	3	3	3	6	6
43	1.65	.	.	.	.	.	9	12	2	.	16	4
34	1.62	.	.	.	.	.	8	.	2	.	2	1
36	1.65	68	25	.	117	72	3	3	3	3	.	.
35	1.76	65	21	.	130	68	0	0	3	3	1	1
28	1.59	52	21	34	100	70	8	3	2	3	13	16
37	1.63	.	.	.	111	75	7	5	2	4	.	.

Pre-eclamptic Women

Age	**Height**	**Pre Weight**	**Pre BMI**	**Neck**	**SBP**	**DBP**	**Women**		**Pre Refresh**	**Preg Refresh**	**Partner**	
							Preg ESS	**Pre ESS**			**Preg ESS**	**Pre ESS**
28	1.62	57	22	34	134	89	4	0	1	4	2	0
31	1.61	72	28	35	156	94	11	4	1	1	10	7
24	1.67	60	22	34	107	83	7	3	1	3	6	3
29	1.69	57	20	34	148	101	5	3	3	3	6	5
28	1.61	57	22	34	111	90	.	.	.	.	.	.
34	1.60	61	24	34	135	87	.	.	.	.	.	.
21	1.57	.	.	36	134	86	.	.	.	.	.	.
31	1.67	64	23	34	120	85	.	.	.	.	4	4
31	1.68	57	20	33	154	89	.	.	.	.	.	.
26	1.68	.	.	36	130	88	5	3	4	4	8	2
34	1.68	76	27	37	130	99	0	0	2	4	3	0
19	1.60	64	25	35	133	77	4	4	1	1	.	.
33	1.70	72	25	38	109	81	11	3	2	3	.	.
31	1.65	67	25	35	121	93	4	3	3	3	9	5
21	1.60	76	30	34	122	84	16	1	3	4	1	1
32	1.57	51	21	33	127	83	8	6	3	4	.	.
34	1.57	55	22	35	132	91	4	0	1	3	4	4
34	1.65	60	22	33	136	86	.	.	.	.	.	.
30	1.60	56	22	33	138	94	.	.	.	.	.	.
19	1.82	92	28	38	146	83	2	.	2	.	.	.
19	1.65	76	28	34	145	95	6	5	1	3	.	.
31	1.78	69	22	35	138	86	10	8	3	4	13	8
42	1.54	54	23	36	127	89	0	0	2	5	3	3
33	1.54	57	24	34	124	85	8	6	3	4	.	.
29	1.60	60	23	34	140	90	11	4	3	4	3	2
21	1.56	65	27	34	128	81	5	5	3	3	.	.
27	1.63	60	23	37	150	95	11	5	3	4	10	6
28	1.73	89	30	38	126	84	9	7	2	4	8	3
27	1.52	.	.	37	.	.	10	6	3	5	.	.
29	1.70	95	33	39	.	.	3	1	1	4	6	2
29	1.65	57	21	34	140	96	8	2	3	5	10	10
30	1.50	62	27	35	150	85	10	3	3	5	.	.
31	1.55	54	22	32	165	90	9	10	3	4	10	7
32	1.59	58	23	36	140	80	3	1	2	3	4	1

37	1.62	89	34	36	160	90	7	2	3	5	8	3
29	1.62	56	21	34	145	99	1	0	4	4	.	.
33	1.65	67	24	34	155	95	4	2	3	5	4	1
35	1.70	79	27	35	130	85	8	9	2	2	7	7
34	1.62	67	26	38	147	92	3	1	4	4	11	8
33	1.60	57	22	36	145	83	8	3	3	4	12	5
29	1.52	57	25	34	140	98	9	8	4	4	11	11
32	1.65	56	21	34	125	80	7	1	3	.	7	3
33	1.70	66	23	34	140	96	10	10	3	4	.	.
34	1.68	.	.	34	150	85	7	3	1	3	.	.
21	1.70	83	29	37	.	.	6	6	.	.	5	9
35	1.63	64	24	36	162	93	.	.	2	2	.	.
.	1.56	.	.	.	.	.	2	2	2	4	.	.
22	1.59	.	.	.	.	.	4	2	4	4	.	.
32	1.71	.	.	.	.	.	0	0	4	5	.	.
33	1.65	.	.	.	.	.	10	4	3	4	.	.
20	1.52	.	.	.	.	.	10	2	1	2	.	.
32	1.56	63	26	34	140	85	5	2	1	4	5	1
26	.	.	.	.	.	.	18	17	2	4	.	.
25	1.52	81	35	42	145	95	7	3	2	2	.	.
18	.	.	.	.	137	92	9	7	2	4	.	.
33	.	.	.	.	123	83	8	3	2	4	.	.
44	1.68	75	27	33	138	96	11	16	1	3	.	.
30	1.76	63	20	37	141	98	5	1	2	4	.	.
34	1.52	.	.	.	135	98	14	8	1	3	.	.
31	1.74	68	22	38	150	102	12	6	3	4	13	.
35	1.65	89	33	37	138	80	4	0	1	4	4	3
29	1.73	57	19	34	127	84	8	4	2	4	3	3
32	1.68	92	33	41	160	90	7	1	3	4	5	1
28	1.72	90	30	37	145	102	10	7	4	5	5	5
21	1.49	48	22	37	140	80	10	4	3	2	9	7
25	1.68	66	23	38	144	95	4	2	3	4	5	4
22	1.63	.	.	41	148	92	3	2	3	4	.	.
35	1.73	81	27	38	138	90	12	12	4	3	12	9
31	1.60	54	21	36	150	98	4	3	2	3	4	3
35	1.65	.	.	38	148	84	7	6	3	4	.	.
37	1.65	67	25	37	155	95	2	2	3	4	6	5
38	1.63	79	30	40	141	70	3	2	4	5	3	1
26	1.72	98	33	40	157	113	1	0	3	4	0	0
39	1.68	69	24	39	140	80	10	4	1	1	.	.
27	1.72	70	24	42	140	110	11	8	2	3	11	6
27	1.60	64	25	36	147	97	0	0	4	3	2	2
30	1.59	66	26	42	155	98	10	4	3	2	3	4
24	1.60	84	33	38	140	85	10	9	2	4	5	4
39	1.68	92	33	42	160	49	5	2	4	5	5	4
32	1.64	60	22	36	130	85	10	2	2	4	9	11
36	1.68	76	27	42	134	98	5	2	4	3	.	.

31	1.65	86	32	41	142	98	6	3	2	4	3	2

Appendix M: Published Papers form this thesis

Izci B, Venelle M, Liston W, Dundas K, Calder A, Douglas NJ. Sleep Disordered Breathing and Upper Airway in Pregnancy and Postpartum. Eur Respir J. 2006;27(2):321-7.

URL: http://ajrccm.atsjournals.org/cgi/content/full/167/2/137

Izci B, Martin S, Dundas K, Liston W, Calder A, Douglas NJ. Sleep Complaints: Snoring and Daytime sleepiness in Pregnancy and Pre-eclamptic Women. *Sleep Med.* 2005;6:163–169.

URL:http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6W6N-4FDJS0P-4&_user=809099&_coverDate=03%2F01%2F2005&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000043939&_version=1&_urlVersion=0&_userid=809099&md5=04aeb26021ae8c37cfd72e44b0ea6689

Izci B, Riha R, Martin S, Venelle M, Liston W, Dundas K, Calder A, Douglas NJ. The Upper Airway in Pregnancy and Pre-eclampsia. Am J Respir Crit Care Med. 2003 Jan 15;167(2):137-40.

URL:http://erj.ersjournals.com/cgi/content/full/27/2/321