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Linking Sleep Disturbance To Idiopathic Male Infertility

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LINKING SLEEP DISTURBANCE TO IDIOPATHIC MALE INFERTILITY

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Summary

Recently published data suggests that male fertility has declined over the past four decades. The reasons for the decline are unclear with up to 50% of cases of male infertility remaining unexplained (idiopathic male infertility). Whilst environmental factors and rising rates of obesity have been implicated, there is now growing evidence that sleep disturbance may be an independent causative factor. Indeed, the prevalence of sleep disturbance appears to be increasing in parallel with deterioration in population sperm quality, a commonly used surrogate marker of male fertility. Although there is some understanding of the relationship between sleep, gonadal hormone secretion and sexual function, it remains to be seen whether sleep disturbance is implicated in idiopathic male infertility. This review will detail the current evidence supporting a link between sleep disturbance and male infertility. Potential mechanistic pathways will be proposed and evidence supporting these pathways will be discussed. Further research is needed in clarifying links between sleep disturbance and idiopathic male infertility. At present the only available treatment option for men with idiopathic infertility is assisted reproductive technology. Demonstration of a causative link between sleep disturbance and idiopathic male infertility may in the future lead to additional treatment options in selected cases.

Keywords

Sleep

Sleep disturbance

Infertility

Obstructive sleep apnea

Reproductive hormones

DNA fragmentation

Male infertility

Abbreviations

AOPP	advanced oxidation protein products
BMI	body mass index
CPAP	continuous positive airway pressure
DFI	DNA fragmentation index
FSH	follicle stimulating hormone
iNOS	inducible nitric oxide synthase
LH	luteinizing hormone
MetS	metabolic syndrome
OSA	obstructive sleep apnea
PCOS	polycystic ovarian syndrome
REM	rapid eye movement
RSD	rapid eye movement sleep deprivation
SpO_2	peripheral blood oxygen saturation
SR	sleep restriction

LINKING SLEEP DISTURBANCE TO IDIOPATHIC MALE INFERTILITY

Introduction

Infertility is commonly defined as the failure to achieve a clinical pregnancy after 12 or more months of regular unprotected sexual intercourse [1]. A review of 28 previously conducted population surveys from different countries found infertility prevalence rates ranging from 3.5% to 16.7% in 'more developed' countries with an estimated overall median prevalence of 9%[2]. Based on Australian data, infertility affects approximately 1 in 6 couples of reproductive age [3]. Of these, 42 percent will have male factors (which is the subject of this review) contributing to their infertility [4]. Of particular concern, a recent systematic review and meta-regression analysis found that surrogate markers of male fertility have declined over the past 4 decades. Moreover, this decline does not appear to be slowing [5] and in up to 50% of cases, the cause remains unexplained. Whilst postulated mechanisms including environmental factors and factors associated with obesity have been linked with this 'idiopathic male infertility' [6], there is emerging evidence that could implicate *sleep disturbance* (impairment in duration and/or quality of sleep) as an important independent factor.

In support of this, it is well recognized that the normal biology of fertility is linked to sleep and circadian biology, suggesting that disturbed sleep might negatively impact on fertility. In fact, several studies have already demonstrated links between sleep disturbance, such as the association of obstructive sleep apnea (OSA) and shift work with reproductive dysfunction. Given that sleep disturbance is common and that its

prevalence is increasing [7], there is good rationale to suggest that it plays an important role in the aforementioned decline in population fertility rates. However, despite some understanding of the relationship between disturbed sleep, male sexual function and gonadal hormone secretion, to date there has been a paucity of research examining the impact of sleep disturbance on male fertility. Regardless, at present, the only available treatment option for men with idiopathic infertility is to circumvent the identified sperm abnormality by way of assisted reproductive technology. Demonstration of a causative link between sleep disturbance and idiopathic male infertility has the potential to significantly impact the management of infertile couples by providing an additional treatment option for selected individuals.

Overview of Review

This review will aim to present a unifying hypothesis that sleep disturbance is an important contributing factor to idiopathic male infertility. Firstly, a brief summary of the important aspects of male reproductive biology and their intimate association with sleep will be summarised. Secondly, the prevalence and significance of male infertility will be highlighted and the epidemiology of sleep disturbance will be covered. The current state of research in fertility and sleep will then be summarised. This will be followed by a discussion regarding the empirical evidence suggesting a link between sleep and idiopathic male infertility, including the increasingly recognised association between obesity and metabolic syndrome (both risk factors for sleep disorders) and male fertility. Potential mechanisms by which sleep disturbance may impact male fertility will then be proposed and supporting evidence will be provided. Finally, the clinical implications of an association between sleep

disturbance and infertility will be explored and future avenues of research will be suggested.

Male Reproductive Biology & Sleep: an overview

Spermatogenesis is under the control of the hypothalamic-pituitary-gonadal axis. GnRH secreted by the hypothalamus stimulates the production and release of FSH and LH by the anterior pituitary. FSH acts on testicular tissue to initiate sperm development and LH acts to trigger testosterone production by Leydig cells within the testes. Testosterone acts on the seminiferous tubules and plays a key role in maintaining spermatogenesis. Indeed, it has been shown that young, sub-fertile men (as defined in this study by sperm concentration < $20x10^6$/mL) have a significantly increased risk of hypogonadism compared to controls [8]. Finally, sperm maturation occurs within the seminiferous tubules, supported by Sertoli cells and takes, on average, 72 days. Mature sperm are transported through the epididymis and vas deferens to the prostate gland. Semen is produced by the prostate gland and seminal vesicles and is the nutrient-rich medium through which sperm is ejaculated [9].

Secretion of testosterone follows a diurnal pattern with maximal levels occurring during sleep [10]. The rise in nocturnal testosterone appears to coincide with the onset of REM sleep and is not related to changes in melatonin concentration (i.e. circadian rhythm) [11]. However, the mechanism by which testosterone secretion is associated with sleep stage is yet to be clearly understood.

Prolactin, secreted by the anterior pituitary gland also plays an important role in male reproductive function. At physiologic levels, prolactin in men enhances the expression of LH receptors in Leydig cells in testicular tissue. This results in testosterone secretion, thus promoting spermatogenesis [12]. Like testosterone, prolactin concentration exhibits a sleep-dependent pattern. Sleep onset is associated with an increase in prolactin secretion and wakefulness coincides with immediate attenuation of active secretion. Furthermore, prolactin secretion appears to be at its lowest at the time of sleep onset [13].

Infertility – population & male-specific prevalence:

Whether the incidence of infertility has been rising in recent times, has been a subject of considerable debate. Measurement of fecundity (the biologic capacity to reproduce, irrespective of pregnancy intentions) and the interpretation of data is challenging. This is because, almost invariably, there is no clear way of distinguishing whether a reduction in birth rates reflect reduced fecundity per se or changes in reproductive behaviour and societal norms (including, for example contraception, delayed child-bearing and access to abortion) [14].

In men, semen parameters have frequently been used in research as a surrogate marker of fecundity. A number of recent studies have examined temporal changes in sperm quality with study periods ranging from 4 to 17 years. Results have generally been conflicting, with some suggesting a gradual decline in sperm concentration and/or total sperm count, and others indicating no significant change or in fact an improvement in sperm parameters [15]. The significant heterogeneity between study

populations could at least partly explain the observed differences. For example, some studies examined young healthy men from the general population whilst others focused on more specific populations such as sperm donors, male partners in infertile couples and fertile men undergoing vasectomy.

A recently published systematic review and meta-regression analysis of 185 studies, comprising in total 42 935 male subjects has presented more convincing evidence of a decline in sperm quality over recent decades. It was shown that between 1973 and 2011 there has been a 50-60% decline in sperm concentration and total sperm count among men unselected by fertility from North America, Europe, Australia and New Zealand [5]. These findings are indeed suggestive of a decline in male reproductive health with potential impacts on fertility. The cause of this decline is yet to be fully explained.

Male infertility - definitions

Traditionally, male infertility has been defined as an abnormality in one or more of the conventionally measured sperm parameters, namely concentration, morphology and motility [16]. Studies have shown, however, that the ability of standard sperm analysis to effectively discriminate between men with high or low fertility is poor [17]. Furthermore, there appears to be significant overlap between infertile men and men with proven fertility with respect to measured values of sperm concentration, morphology and motility [18].

One possible explanation for the low predictive value of standard sperm parameters in identifying male infertility is the marked intra-individual variability of these measures even within one spermatogenic cycle (approximately 10 weeks) [19]. It is thus generally recommended that an abnormal semen analysis be repeated at least once [16]. Another possible contributing factor is that standard sperm analysis is mainly performed manually by light microscopy on a representative sample of spermatozoa (usually 200-400) [16]. This results in a high degree of subjectivity and potential for significant inter-laboratory and intra-laboratory variation.

In recent years, sperm DNA fragmentation has been suggested as a more reliable objective measure of sperm quality than the standard sperm parameters described above [20]. DNA fragmentation (quantified by a sperm chromatin structure assay) is a measure of sperm damage and oxidative stress is considered to be an important underlying cause [21]. Utilising flow cytometry and acridine orange staining of single-stranded DNA at sites of DNA strand breakage, this technique has the ability to collect data on 5000 or more spermatozoa within minutes [22]. The DNA Fragmentation Index (DFI) is a measure of the degree of DNA fragmentation expressed as a percentage of the total sperm count.

High levels of sperm DNA fragmentation are strongly associated with male infertility in both assisted conception cohorts and normal populations [23, 24]. The Georgetown Male Factor Infertility Study examined 165 healthy couples attempting natural conception. It established DFI ranges categorising fertility potential as excellent (≤15%), good (>15 to <30%) and fair to poor (≥30%), based on the odds ratio of conception [25]. Similarly, a Danish population study of 215 couples with no

previous history of infertility demonstrated that a DFI > 20% significantly decreased the chance of spontaneous pregnancy. As DFI approached 40%, spontaneous conception was negligible [26].

Interestingly, studies examining the correlation between standard sperm parameters and DNA fragmentation have yielded conflicting results [27-29]. Nevertheless, up to 40% of men have been shown to have a DFI > 20-30% despite normal sperm parameters based on WHO criteria [27, 30, 31]. This suggests that conventional semen analysis does not encompass all aspects of semen quality and DFI is an important and useful adjunctive tool in the assessment of male infertility. Furthermore, it also indicates that couples who have in the past been labelled as having 'unexplained' infertility (i.e. no male or female cause identified) may indeed have had abnormally high levels of sperm DNA fragmentation contributing to their infertility.

Causes of male infertility & significance of idiopathic male infertility:

There are a number of underlying causes of male infertility. These can be categorised into 1) genetic factors (e.g. congenital absence of vas deferens, cryptorchidism and karyotype abnormalities); 2) acquired factors (e.g. recurrent urogenital infection, trauma, testicular torsion, varicocele, urogenital obstruction, systemic diseases, medication, irradiation) and 3) idiopathic. The importance of idiopathic infertility has been largely under-recognised. Indeed, it has been suggested that approximately 50% of men with documented infertility have no identifiable cause [6]. A number of possible underlying mechanisms for idiopathic

male infertility have been postulated. These include environmental toxins, smoking, scrotal hyperthermia, mobile phone radiation and yet to be identified genetic factors. There has also been considerable interest in the potential role of obesity and metabolic syndrome as possible contributing factors in idiopathic male infertility.

Obesity & male infertility

Several large epidemiological studies have demonstrated an association between infertility and male overweight and obesity after adjustment for a variety of confounding factors. Most studies show a 'dose effect' with higher BMIs (body mass index) correlating with increased odds of infertility [32-34]. Evidence of an association between obesity and male infertility from studies of couples seeking fertility treatment is more conflicting. Hanafy et al [35] studied 80 male partners among infertile couples and demonstrated BMI in infertile men with reduced sperm concentration was only slightly higher (and not statistically significant) than fertile men with normal sperm concentration [35]. Another study examined 72 infertile couples and classified male partners into 3 groups: male factor sub-fertility, idiopathic subfertility and female factor subfertility. Obesity (BMI≥30kg/m2) was 3 times more common in the male factor subfertility group [36]. Variability in the study results could be accounted for by differences in patient selection. For example, Hanafy et al [35] classified subjects as being infertile based on sperm concentration only. On the other hand, Magnusdottir et al [36] required subjects to have abnormalities in at least two out of 3 domains of sperm quality, namely, sperm concentration, total sperm count and progressive sperm motility, for them to be included in the male factor sub-fertility group.

Results obtained from studies examining the relationship between obesity and sperm quality have been similarly-conflicting. A 2010 meta-analysis of 31 studies found no evidence of an association between increasing BMI and sperm concentration or total sperm count [37]. On the other hand, another meta-analysis of 21 studies conducted 3 years later demonstrated that compared with men of normal weight, the odds ratio (95% confidence interval) for oligozoospermia (low sperm concentration) or azoospermia (no sperm detected on at least two separate occasions) was 1.11 (1.01-1.21) for overweight, 1.28 (1.06-1.55) for obese and 2.04 (1.59-2.62) for morbidly obese men [38]. Studies examining the relationship between male obesity and other traditional sperm parameters such as motility and morphology have also yielded variable results. These differences in study results may possibly be explained by the relatively poor predictive value of standard sperm parameters in identifying male infertility as previously discussed. Interestingly, in contrast, numerous studies have demonstrated a relationship between male obesity and reduced sperm DNA integrity [39-43] a measure that is considered to be a more accurate marker of impaired male fertility. In addition, two studies have demonstrated an association between obesity and increased levels of sperm oxidative stress (considered to be an important cause of DNA fragmentation and male infertility) although interpretation of both studies is limited by small sample size [44, 45].

It is well recognised that significant weight loss (either by low-calorie diet or bariatric surgery) results in marked improvements, and in some cases, normalisation of gonadal hormone levels in severely obese men [46]. These improvements appear to

be correlated to degree of weight loss and reductions in waist circumference. Furthermore, bariatric surgery appears to be more effective than low energy diets in increasing testosterone levels [46]. Whether weight loss results in improvements in sperm quality, on the other hand, remains uncertain. Several observational studies have examined this question with conflicting results. Some studies show improvements in various sperm parameters with weight loss [47-50], whilst at least one study showed no change [51]. There have also been anecdotal reports of surgical weight loss resulting in a deterioration in sperm quality [52, 53]. These differences may be due, at least in part, to heterogeneity in patient populations (e.g. obese patients undergoing bariatric surgery vs male partners of sub-fertile couples), weight loss method (surgical vs life-style intervention), baseline sperm parameters, follow-up period and sample size. Furthermore, whether observed improvements in sperm quality are related to weight loss per se or other confounding factors e.g. lifestyle change or improved metabolic profiles remains to be elucidated.

A number of potential mechanisms linking obesity and male infertility have been proposed. These include hormonal derangements, accumulation of environmental toxins and endocrine disruptors in fatty tissue; increased testicular temperature related to prolonged sitting as well as erectile dysfunction [54]. Recently however, there has been interest in the possible role of obstructive sleep apnoea as a modulating factor in obesity and infertility [55]. However, to date there have been no studies that have examined the prevalence of OSA in infertile men. This is surprising given that current evidence suggests a number of theoretical mechanisms by which OSA may impact sperm quality and function. These mechanisms will be covered later in the review.

Metabolic Syndrome & male infertility

It has been suggested that metabolic syndrome (MetS) may have direct effects on male fertility [56]. A recent case-controlled study of 42 men with MetS and 32 controls found significant reductions in ejaculation volume, sperm concentration, total sperm count and progressive and total motility in the MetS group. Furthermore, there were significantly higher values of DNA fragmentation in men with MetS [57]. In another study, men with metabolic syndrome were found to have 9% lower total testosterone, 11% lower calculated free testosterone, and 18% lower sex hormone-binding globulin (a glycoprotein that binds androgen and estrogen) than controls [58]. What remains to be explained is which characteristic(s) of MetS contribute to this apparent impairment of reproductive function and whether the observed abnormalities correlate with reduced fertility potential. Of course, male infertility and its association with obesity (a cardinal feature of MetS) has been extensively studied however the impact of other features of MetS on male fertility is less well understood. Despite the direction of causality being a matter of ongoing debate [59, 60], it is well recognised that MetS is strongly associated with OSA [61-63]. There is also now emerging evidence of links between chronic sleep restriction, obesity and MetS [64-66]. It is thus possible that OSA or chronic sleep restriction in people with MetS acts as a modulating factor in the observed impairments in male fertility.

Epidemiology of Sleep Disturbance:

The growing prevalence of a '24/7' society with 'round the clock' provision of services and entertainment suggests that, on a population level, circadian disruption leading to impairments in duration and/or quality of sleep (sleep disturbance) may increase in the future. Certainly, night-time use of electronic devices (cell-phones, computers and televisions) is common-place [67]. Use of such devices has been shown to have a dose-dependent association with delayed sleep/wake schedules [67]. Furthermore, blue-light exposure from LED (light-emitting diode) devices is associated with a reduction and delay in melatonin secretion [68], decreased subjective and objective sleepiness [68, 69] and prolonged sleep onset latency [69].

Supporting these observations are findings from the 2016 Sleep Health Survey conducted by the Sleep Health Foundation of Australia. The survey studied over 1000 Australian adults with regards to the health and social consequences of sleep disturbance and specific sleep disorders (OSA and insomnia). It was found that over one quarter of all adults (26%) use the internet on most or every night of the week just before bed with associated frequent sleep difficulties or daytime impairments. Furthermore, 23% reported that their usual daily activities (work or home duties) do not allow them to obtain sufficient sleep. This figure rose to 30% in the subgroup of respondents aged between 18-44yo (i.e. those of prime reproductive age). When compared to the results of an earlier survey in 2010 it appears that the prevalence of sleep difficulties and daytime consequences has increased over this time, although direct comparison is limited somewhat by differences in study methodologies between the two surveys [7].

With respect to the epidemiology of specific sleep disorders, it is well known that the prevalence of OSA is increasing in parallel with rising rates of obesity [70]. OSA prevalence estimates vary between studies depending on the age and sex distribution of the study population as well as the criteria used to diagnose OSA. Nevertheless, a recent meta-analysis of 24 studies found the general population prevalence to be between 9% and 38% with prevalence being greater amongst men [70]. Of relevance to a discussion on male fertility, the age-specific prevalence of OSA in male subjects in the 30-39 age-group has been shown to range from 9.7% [71] in one study to 38.3% [72] in another (based on an apnea-hypopnea index {AHI} of ≥ 5/hr for diagnosis of OSA). The apparent difference in prevalence between the two studies may be accounted for by heterogeneous population sampling methods and a low response rate for polysomnography in non-habitual snorers in one study [71]. Regarding insomnia, the 2016 Sleep Health survey estimated a prevalence of 16.7% in men, based on ICSD-3 criteria [7] and in shift-workers (rotating or night-shift), the prevalence of shift-work disorder (as defined by the presence of insomnia and excessive sleepiness based on DSM-IV and ICSD criteria) was estimated to be approximately 10% in one large epidemiological study [73].

Thus, it is evident that disturbed sleep is emerging as an important public health issue in contemporary society. With evidence indicating a concomitant deterioration in male reproductive function over recent decades, it is somewhat surprising that the impact of sleep disturbance on male fertility has been a largely neglected area of research to date.

Infertility & sleep disturbance: Current state of research

Most research conducted in the area of fertility and sleep disturbance has focused on females. For example, polycystic ovarian syndrome (PCOS), a common cause of female infertility characterised by anovulation, hyperandrogenemia and high rates of insulin resistance and obesity, has been associated with an increased prevalence of sleep-disordered breathing, independent of obesity [74, 75]. Furthermore, in one small, uncontrolled study, successful treatment of OSA with continuous positive airway pressure (CPAP) was shown to mitigate the cardio-metabolic sequelae associated with PCOS [76].

In the setting of shift-work, prolonged time to pregnancy (a surrogate marker of fertility) [77] and reduced ovarian reserve [78] have been reported. Additionally, an increased risk of pregnancy complications such as miscarriage and low birth-weight have been suggested in some early studies [79, 80]. However, a recent meta-analysis suggests this risk is smaller than previously thought [81].

The majority of published studies in men focus on the impact of sleep-disordered breathing on gonadal hormones (mainly testosterone). Certainly, several studies have demonstrated a negative correlation between testosterone levels and sleep apnoea, independent of BMI [82, 83].

Early research demonstrating a relationship between sleep-related erections and testosterone levels [84] led to further work supporting an association between sleep-disordered breathing and erectile dysfunction. Indeed, it has been shown that erectile dysfunction occurs in half of all men with OSA, independent of obesity [85].

Despite some understanding of the relationship between disturbed sleep, male sexual function and gonadal hormone secretion, it remains to be elucidated whether these putative mechanisms translate to clinically significant effects on male fertility. In particular, little is known regarding the effects of the various sequelae of sleep disturbance (sleep fragmentation, sleep restriction, circadian disruption or hypoxia) on male reproductive capacity (Figure 1).

Sleep & idiopathic male infertility – empirical evidence of an association

A recent observational study of 953 young Danish men from the general population lends empiric support to the hypothesis that sleep disturbance is a causative factor in idiopathic male infertility. It found an association between levels of sleep disturbance (as measured by a modified 4-item version of the Karlolinska sleep questionnaire) and measures of sperm quality. Men with a high level of sleep disturbance (questionnaire score >50), had a 29% lower adjusted sperm concentration and 1.6% fewer morphologically normal sperm compared with men with a sleep score of 11-20 [86]. This study did not however identify the underlying causes of sleep disturbance such as obstructive sleep apnea, short sleep duration or shift-work which will be covered below.

Obstructive Sleep Apnea

To our knowledge, there have not been any published studies examining whether an association exists between OSA and male infertility. Nevertheless, the relationship between OSA and reproductive hormone profiles has been studied, particularly in

relation to testosterone. Indeed, aberrations in gonadal hormone secretion in the context of OSA, as detailed below, may serve as a marker of fertility impairment.

One small study of the impact of OSA on male sexual function examined 24 consecutive men referred for sleep studies. Significantly lower serum testosterone levels were found in 15 men with OSA (Apnea index > 5/hr) compared with 9 non-OSA snorers [87].

Gambineri et al [82] measured total and free testosterone in 15 obese male subjects (BMI >30kg/m2) with obstructive sleep apnoea syndrome (Epworth sleepiness score > 10 and apnea hypopnea index >10/hr on polysomnography) and 15 age and BMI matched controls. Both total and free testosterone levels were significantly lower in the sleep apnoea group compared to controls. This relationship persisted after adjusting for BMI and waist circumference [82]. A more recent study of 89 severely obese men (BMI ≥35kg/m2) demonstrated a 'dose effect' with increasing OSA severity (as measured by AHI) being correlated with progressively lower serum free testosterone levels after correction for age and BMI. Furthermore, other measured parameters such as time spent below peripheral blood oxygen saturation (SpO_2) of 90% and time spent below SpO_2 of 80% were also inversely related to testosterone levels [83] suggesting that hypoxia might be an important factor. In contrast, a small study of 5 middle-aged obese men with OSA, compared with five age and BMI matched controls and 6 lean healthy young controls found that differences in testosterone levels were a function of obesity and age rather than OSA [88].

Studies have also assessed the impact of OSA therapy on reproductive hormones but they have yielded conflicting results. This is possibly related at least in part to

small sample sizes and, for the most part, observational study designs. Grunstein et al [89] studied 43 men with severe OSA and found that 3 months of CPAP therapy led to a significant improvement in total testosterone levels, independent of weight loss.[89] Similarly, a small study of 5 men with OSA found that 9 months of CPAP therapy was associated with a partial correction of mean and area-under-curve testosterone [90]. On the other hand, a more recent 6-month study of 67 men with severe OSA found that CPAP therapy was not associated with improvement in total testosterone [91]. A significant limitation of this study, however, was that baseline testosterone levels prior to CPAP therapy were within the normal range. Other studies in this area, including the only randomized sham-controlled trial, have been limited by a relatively short duration of CPAP therapy (≤ 1 month) which may have under-estimated the effect size [92, 93]. Interestingly, in a prospective study of 12 men with moderate to severe OSA (and low testosterone levels) significant improvement in serum testosterone was noted 3 months after undergoing uvulopalatopharyngoplasty surgery to correct OSA. The observed change was not associated with a significant reduction in BMI however it did appear to be related to improvement in several measures of sleep-disordered breathing [87].

The mechanism underpinning the association between OSA and low testosterone levels is yet to be clearly elucidated. Nocturnal hypoxaemia leading to changes in the hypothalamic-pituitary gonadal axis has been suggested as a potential cause. Supporting this hypothesis, Kouchiyama et al [94] found that more severe nocturnal oxygen desaturation in OSA was associated with a delayed peak testosterone level and total desaturation time was negatively correlated with serum testosterone levels [94].

Other study findings have suggested sleep fragmentation as a possible underlying mechanism to explain reduced testosterone levels in OSA. In one study, 10 healthy young men were subjected to 24 hours of fragmented sleep using the previously described 7/13 ultrashort sleep paradigm [95]. It was found that sleep fragmentation was associated with a blunted nocturnal rise in testosterone. Testosterone secretion occurred in concert with REM sleep and interestingly, no testosterone rise was noted in 5 men who had a complete absence of REM sleep over the 24-period [11].

With respect to prolactin, studies examining its secretion in the context of OSA have yielded mixed results. For example, Grunstein et al [89] found that plasma prolactin levels were not significantly different in men with OSA versus men without OSA in a cross-sectional study of 225 consecutive subjects undergoing sleep studies. Furthermore, three months of nasal CPAP treatment did not result in a significant change in prolactin concentration [89]. Similarly, Meston et al [93] found no correlation between OSA severity and prolactin levels in a cohort of 101 men with OSA. Subjects were then randomised to therapeutic nasal CPAP or sham CPAP for one month but no difference in prolactin levels between the two groups was observed [93].

A significant limitation to these studies is that prolactin levels were taken as single measures during periods of wakefulness. Normal day-time levels do not necessarily equate to normal sleep-related levels of prolactin in OSA subjects. One particular study examined the sleep-related pattern of prolactin secretion in 7 treatment-naive male subjects with severe OSA. Blood samples were taken at 10-minute intervals

and prolactin secretory rates were calculated by a deconvolution procedure. Subjects underwent two overnight studies (separated by a week) one without treatment and the other with CPAP therapy. The secretory pulse amplitude and total prolactin secretion remained unchanged however there appeared to be a lower pulse-frequency in untreated OSA as compared to treated OSA patients. One night of CPAP therapy was not only found to restore sleep architecture but also normalise prolactin pulse frequency to values similar to those observed in historical controls [96].

Postulated mechanisms linking abnormal prolactin secretion and OSA have included both sleep fragmentation and hypoxia. Indeed, acute hypoxia has been shown to have an inhibitory effect on prolactin secretion [97, 98], but whether similar effects are observed in the setting of chronic repetitive hypoxia (as is observed in OSA) is yet to be elucidated. The impact of sleep fragmentation on prolactin secretion is less well studied. Nevertheless, the normalisation of sleep architecture and prolactin secretory patterns after one night of CPAP therapy [96] suggests that sleep fragmentation may indeed play a role.

Short sleep duration

Empirical evidence demonstrating a link between sleep duration and male fertility is scarce. At the recent American Society for Reproductive Medicine 2016 meeting, Wise et al [99] presented an abstract of a web-based prospective cohort study of 695 couples in USA and Canada examining among other things, the extent to which duration and quality of sleep influences male fecundability. At enrolment, all couples had been attempting to conceive for 6 or fewer cycles. An inverted U-shaped relation

was observed between sleep duration and male fecundability. Relative to 8 hours of sleep per night, fecundability ratios were reduced in subjects who obtained less than 6 or more than 9 hours of sleep per night. Compared with men who reported no trouble sleeping, fecundability ratios were also reduced in subjects reporting trouble sleeping 'slightly more than half of the time, most of the time or all of the time' [99].

Shift-Work

The impact of circadian disruption (such as occurs in rotating shift-work) on male fertility is yet to be fully elucidated. In a large European multi-centre epidemiological study of shift-work and subfecundity, no association between male shift-work and fecundity was observed [100]. Similarly, a more recent observational prospective cohort study of 501 couples attempting to conceive found no association between night work or rotating shift-work and semen quality (including DNA fragmentation index) [101]. This is in contrast to an earlier case control study of 255 infertile men and 267 male controls with proven fertility, which demonstrated an association between male infertility and shift work (OR 3.60, 95%CI: 1.12-11.57) [102].

Similarly, the effect of shift-work on reproductive hormone secretion in men is not fully understood. Night-time secretory patterns of testosterone and prolactin in 12 male oil refinery workers on a fast rotating shift system (every 3-4 days) was studied by Touitou et al [103]. Blood samples were taken every 2 hours from 0000 to 0800. Marked changes in the secretory profiles of both prolactin and testosterone was observed with erratic peak and trough times as well as reduced serum concentrations of the two hormones. Secretory patterns of gonadal hormones during day-time sleep however was not studied [103]. In another study, night-shift workers were observed to have delayed peak testosterone production in comparison to day-

workers [104]. These abnormalities in reproductive hormone secretion in shift workers may indeed be associated with impaired fertility however this is yet to be studied.

Sleep & idiopathic male infertility – potential mechanisms

Hypoxia & oxidative stress

High levels of sperm DNA fragmentation are a strong predictor of male infertility and oxidative stress is considered to be an important contributing factor. In this context, repetitive nocturnal hypoxia as a result of recurrent obstructive apnoeas has been associated with increased levels of oxidative stress. Evidence of oxidative stress in OSA includes studies showing (1) enhanced release of superoxide from leucocytes; (2) reduced bioavailability of nitric oxide; (3) reduced anti-oxidant capacity and (4) increased oxidation of biological compounds such as lipids, proteins and DNA [105]. Thus, it is biologically plausible that OSA may have a direct impact on sperm quality and fertility potential, mediated through hypoxia-induced sperm DNA damage This effect of OSA on sperm quality may be independent of the known effects of obesity on oxidative imbalance and sperm DNA fragmentation.

Torres et al [106] recently tested the hypothesis that male fertility is reduced in mice by exposure to chronic intermittent hypoxia mimicking OSA. In this case-control study, mice were subjected to either a pattern of periodic hypoxia (20 seconds at 5% O2 followed by 40s of room air) or continuous normoxia. The mice then performed a

mating trial to determine fertility (quantified by the number of pregnant females and total number of foetuses). After euthanasia, oxidative stress within testicular tissue was assessed in both groups by measurement of expression of the anti-oxidant enzymes, super-oxide dismutase-1 and glutathione peroxidase-1. It was found that intermittent hypoxia was associated with a significant reduction in the expression of both enzymes by over one-third. Progressive sperm motility was significantly reduced in the intermittent hypoxia group compared to the group exposed to normoxia. Furthermore, fertility was significantly lower in the hypoxia group compared with the control group as evidenced by a reduced number of pregnant females per mating and a lower number of fetuses per mating [106].

To date, the effect of hypoxia on sperm quality has only been studied in humans in the setting of altitude exposure (hypobaric hypoxia). It has been demonstrated in several studies that chronic hypobaric hypoxia results in reversible fertility impairments in non-adapted individuals [107-109]. For example, in one recent study, semen parameters of six healthy male mountain trekkers were first evaluated in normoxic conditions at sea-level. The study subjects then undertook 26 days of altitude exposure (2000 to 5600m) following which repeat semen analysis was performed after their return to sea level. Sperm count, percentage of abnormal or immature spermatozoa and total numbers of motile sperm in the ejaculate were found to be significantly lower immediately following return from the expedition and also after 1 month. Levels of all 3 parameters returned to baseline after 6 months. Reduction in sperm motility was observed 1 month following return having been normal immediately post-expedition. At 6 months, motility had returned to pre-hypoxic exposure levels.[108] A recent study of seven male mountaineers found that even short-term (five days) exposure to altitude hypoxia can significantly reduce

sperm forward motility. It was hypothesised that in addition to the direct effects of hypoxia on sperm production, spermatozoa may also be susceptible to hypoxia during their transit through the epididymis where they mature and acquire motility [110]. Of course, the pattern of hypoxia experienced at altitude is somewhat different to that observed in OSA. Furthermore, increased hypoxic-ventilatory drive at altitude is known to precipitate periodic breathing and central sleep apnoea [111]. Apart from hypoxia, other factors such as sleep disturbance and weight change may have also contributed to changes in sperm factors. Overall, it is yet to be elucidated whether nocturnal sleep-disordered breathing contributes to the observed effects of altitude exposure on male fertility.

In contrast to humans, studies in rats have shown chronic hypobaric hypoxia to induce a state of local oxidative stress within testicular tissue with concomitant changes in testicular morphology and loss of spermatogenic cells, via apoptosis in all stages of the cell-cycle [112]. This may then lead to altered fertility by way of reduced sperm production and DNA damage.

Systemic inflammation

Several studies have demonstrated increased levels of pro-inflammatory cytokines to have detrimental effects on spermatogenesis, sperm quality and fertility [113-115]. In relation to sleep disturbance, there is growing evidence suggesting that, in some circumstances, it may induce a pro-inflammatory state. For example, OSA is shown to be associated with elevations in inflammatory markers such as interleukin-6 (IL-6), tumour necrosis factorα (TNFα) and C-reactive protein [63, 116]. Sleep restriction has also been linked to elevations in these inflammatory markers in both human and

animal studies [117-121]. Furthermore, Leproult and colleagues have found that circadian misalignment augments systemic inflammation (as measured by high sensitivity CRP), independently of sleep loss [122]. Thus, it is plausible that systemic inflammation induced by disturbed sleep may impact reproductive function and possibly, fertility (Figure 1).

In the context of metabolic syndrome and its strong association with OSA, Leisegang and colleagues [123] found both serum and seminal concentrations of pro-inflammatory cytokines, IL-6, IL8, TNFα and IL-1β to be elevated in male subjects with MetS, compared with controls. These elevations were associated with significant impairments of fertility including reduced ejaculation volume, sperm concentration and motility as well as an elevated DFI. Increased seminal concentrations of the pro-inflammatory cytokines occurred in the absence of identifiable infection or other cause of local inflammation. The authors hypothesised that the increased seminal inflammatory cytokines occurred as a result of serum cytokines passing into the reproductive tract in the setting of increased serum concentrations. It is indeed possible that the observed association between MetS, inflammatory markers and sperm quality actually reflects the effect of comorbid sleep disturbance (either OSA or chronic sleep restriction), with systemic inflammation impacting the local testicular micro-environment, resulting in impaired fertility.

Insulin resistance & dyslipidaemia

Although a clear causal relationship between OSA and dyslipidaemia has not been firmly established, there is a substantial amount of evidence demonstrating an association between the two conditions. Furthermore, OSA severity may correlate

with severity of dyslipidaemia [124]. Similarly, OSA has been shown to be associated with insulin resistance, independent of obesity [125].

The effects of insulin resistance and dyslipidaemia on markers of fertility has been largely studied in the context of metabolic syndrome. Insulin resistance in particular has been shown to correlate negatively with serum testosterone levels [126]. However, whether these observed changes in testosterone secretion translate to impairements in male fertility is yet to be determined.

With respect to dyslipidemia, Shalaby and colleagues studied the effects of a high cholesterol diet as well as cholesterol-lowering therapy on the fertility of male rats. A high cholesterol diet was associated with significant reductions in fertility, testicular weight and traditional measures of sperm quality (concentration, motility, viability). Interestingly, administration of either α-tocopherol, (a potent anti-oxidant) or simvastatin (a lipid-lowering agent) resulted in improvements in all measured domains of sperm quality as well as fertility [127]. The effect of anti-oxidant therapy in improving fertility in this study supports the possibility that dyslipidemia induces oxidative stress locally within the testes leading to sperm DNA damage and infertility.

Sleep restriction

Sleep restriction is a feature in several sleep disorders including OSA, shift-work disorder and insomnia and is a possible mechanistic pathway leading to male infertility.

Sleep restriction has been shown to alter gonadal hormone levels in an experimental setting. For example, testosterone levels were found to be reduced in 10 healthy male volunteers subjected to 1 week of sleep restriction (5 hours of sleep per night) [128]. In another study of 15 healthy men it was found that 4.5 hours of sleep restricted to the first half of the night (22:30 to 03:30h) was associated with a significant reduction in testosterone concentrations. This was in contrast to subjects restricted to 4 hours of sleep in the second half of the night (02:45-07:00h) who did not experience significant changes in testosterone levels [129]. The effect of sleep deprivation on gonadal hormone secretion has also been examined. Several studies have consistently demonstrated significant reductions in testosterone secretion following 24-48 hours of total sleep deprivation in controlled conditions [130-132].

Whether sleep restriction or sleep deprivation has direct effects on testicular function and spermatogenesis in humans remains to be answered. A recent study in rats however suggests that this may be the case. Alvarenga et al [133] evaluated the effect of sleep restriction (SR) and REM sleep deprivation (RSD) on sperm parameters and testis-specific gene expression in male rats. When compared to a control group of rats, both RSD and SR groups had lower sperm viabilities and significantly fewer spermatozoa with fast progressive motility. Regarding testicular gene expression, both RSD and SR led to increased expression of inducible nitric oxide synthase (iNOS) compared to the control group. iNOS is a potent free radical that contributes to oxidative stress. An increase in the expression of 11β-dehydrogenase-1 was also observed with RSD and SR. This enzyme reduces cortisone to the active hormone, cortisol and increased expression may be considered a surrogate marker of the physiological ‘stress’ response [133].

A similar study by Choi et al [134] found that sleep deprivation of either 4 or 7 days in male rats was associated with a significant decrease in testosterone levels. Furthermore, there was a statistically significant reduction in sperm motility (but not concentration) in rats subjected to 7 days of sleep deprivation compared to the control group.

Circadian disruption

From a mechanistic perspective, melatonin, a key circadian hormone, is known to influence the synthesis and release of hypothalamic GnRH and thus pituitary LH and FSH and eventually testicular function. It is also recognised as a potent anti-oxidant. In addition to these actions, it has recently been suggested that melatonin has a direct effect on testicular function. Rossi et al [135] demonstrated that melatonin concentrations in human testicular biopsies of men with idiopathic infertility were negatively correlated with macrophage concentration and expression of pro-inflammatory cytokines (TNFα and IL1β) but positively correlated with expression of anti-oxidant enzymes (superoxide-dismutase-1, catalase, peroxiredoxin). Furthermore, in primary cell culture of hamster testicular macrophages, they found melatonin to increase the expression of anti-oxidant enzymes and decrease reactive oxygen species generation [135]. In another study, markers of oxidative protein damage (advanced oxidation protein products, AOPP) were correlated with melatonin levels in the seminal plasma of men with azoospermia (complete absence of sperm), teratozoospermia (<4% normal sperm morphology) and fertile controls. Levels of melatonin were significantly reduced and AOPP concentrations increased in both azoospermic and teratozoospermic groups compared to fertile controls [136].

These studies lend weight to the theory that disruption of melatonin secretion (as occurs in rotating shift-workers, for example) may impact on testicular function and fertility by causing oxidative imbalance locally within the testes, thus increasing susceptibility to sperm DNA damage. This implies that melatonin supplementation could be used in the setting of male infertility and co-existent sleep disturbance to improve sperm quality. Indeed, in the reproductive medicine sphere, there has been increasing interest in the potential role of melatonin supplementation as an adjunctive treatment for men with otherwise unexplained infertility. Although large scale prospective trials have not been undertaken the findings of one recent study of 30 infertile men recruited from a fertility clinic suggests a possible beneficial role [137]. Following administration of melatonin 6mg nightly for 90 days, a significant reduction in DNA fragmentation rates and improvement in embryo quality during subsequent in-vitro fertilization cycles was observed. Furthermore, an increase in both urinary and seminal total anti-oxidant capacity was noted.

Clinical implications

Sleep disturbance is a growing problem of modern society that in recent years has been found to have significant, deleterious effects on cardio-metabolic and neurocognitive function. Paralleling the increase in sleep disturbance has been an apparent deterioration in male reproductive function and potentially fertility. Indeed, it is possible that sleep disorders such as OSA, insomnia and shift-work disorder could be causative factors in male idiopathic infertility however this remains to be elucidated. Certainly, there is a breadth of theoretical evidence which supports several possible mechanistic pathways linking sleep and male fertility (Figure 1).

Up until this point, discussion has focused on the potential modifying influence of sleep disturbance on male fertility. It is important to highlight, however that the relationship between sleep disturbance and male fertility may be bi-directional in nature. For example, it is well recognised that the experience of infertility is associated with marked levels of stress in both men and women. Data on the male experience of infertility is less abundant than that in women however qualitative research does reveal depression, isolation and shame to be common themes [138]. Depression and anxiety in turn can have notable negative effects on sleep quality. However, the opposite is also true: sleep disturbance can affect mental health. Therefore, it is possible that a vicious cycle could exist whereby sleep disturbance and infertility exacerbate one another. Interestingly, in one study of 112 subfertile men, sperm count, semen volume and serum testosterone levels were negatively correlated with depression and anxiety scores as measured by validated questionnaires [139]. Several other studies have also found associations between psychological stress and sperm quality [140-142].

Research agenda & conclusions

To our knowledge there have been no published studies in humans examining the relationship between sperm quality and the various domains of sleep disturbance. Moreover, the epidemiology of sleep disorders in men with otherwise unexplained infertility remains unknown. Further research is required in both regards.

Indeed, at the very least, greater recognition of sleep disturbance in infertile men, together with therapeutic interventions directed towards improving sleep health may assist in ameliorating psychological distress during their infertility journey. Furthermore, if a causal relationship between specific sleep disorders and sperm quality is demonstrated, it is plausible that treatment of these sleep disorders may improve sperm quality and possibly, fertility. This has the potential to impact significantly on the current treatment paradigm of otherwise unexplained male infertility by providing an additional treatment option for selected individuals who are attempting to conceive.

Conflict of Interest

None to declare.

Practice Points

1) Evidence suggests that male fertility has declined significantly over recent decades, the reasons for which remain unclear. Sleep and circadian biology are intimately linked with the normal biology of fertility therefore it is plausible that sleep disturbance negatively impacts on fertility.
2) Although there is some understanding of the relationship between male reproductive hormones, sexual function and sleep disturbance, it remains to be shown whether a relationship exists between disturbed sleep and male fertility. In particular, the impact of the various domains of sleep disturbance (hypoxia, circadian disruption, sleep fragmentation and sleep restriction) on male fertility is not fully understood.
3) Potential mechanistic pathways linking sleep disturbance and idiopathic male infertility include hypoxia, oxidative stress, systemic inflammation, aberrant reproductive hormone secretion, insulin resistance and dyslipidaemia.
4) Observed impairments in male fertility and reproductive function in the setting of obesity and metabolic syndrome may be modulated by comorbid sleep disorders such as obstructive sleep apnea or short sleep duration.

Research Agenda

1) Prospective observational studies amongst men with idiopathic infertility are necessary to determine the prevalence of sleep disorders such as obstructive sleep apnea, shift-work disorder and insomnia in this population. Greater recognition of comorbid sleep disturbance will allow the institution of appropriate therapy directed at improving sleep, which at the very least will improve patient well-being during a time that can be particularly stressful for individuals and couples.
2) Randomized-controlled studies examining the effect of treatment of specific sleep disorders on appropriate surrogate markers of male infertility (e.g. sperm DNA fragmentation index) are necessary to determine whether sleep disturbance causes idiopathic male infertility. Larger placebo- and sham-controlled studies will then allow assessment of the efficacy of directed treatment of sleep disorders in improving male fertility in selected cases. This has the potential to open up additional therapeutic options for men with idiopathic infertility and comorbid sleep disturbance.

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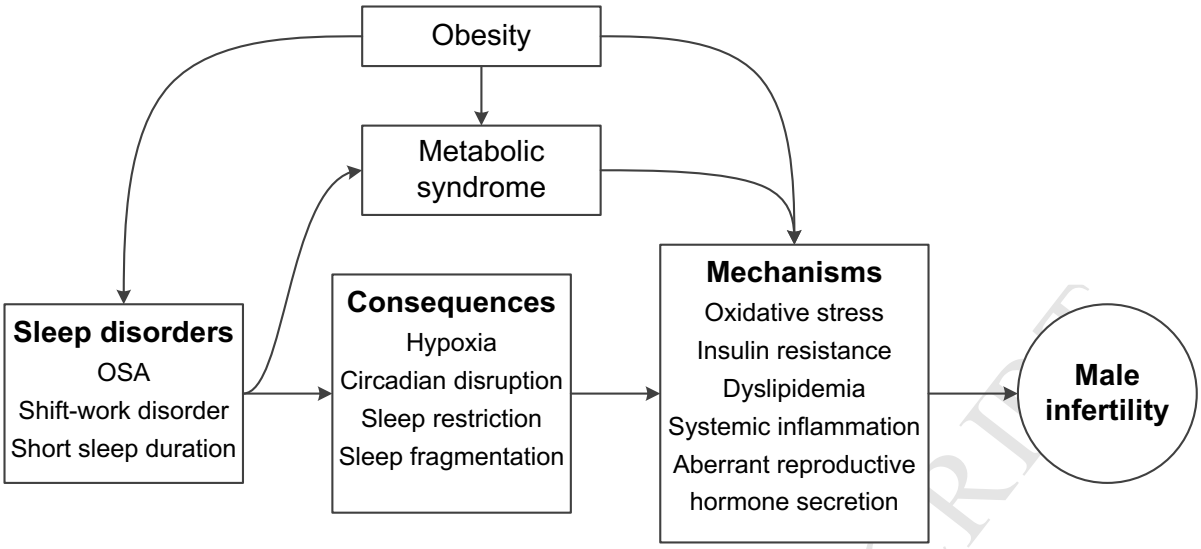

Figure 1.

The consequences of common sleep disorders and the plausible mechanisms by which they may lead to male infertility. The role of obesity and metabolic syndrome in male infertility (independently and through their association with sleep disorders) is also illustrated.