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Psychological aspects of infertility: A systematic review

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Abstract

Objective: Fertility may be defined as a capacity to conceive and produce offspring. Infertility is characterized by failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse. Infertility concerns an estimated 8–12% of the global population, and is associated with factors including time of unwanted non-conception, age of female partner and number of diseases impacting fertility. Unexplained infertility is described as idiopathic. This study aimed to analyse and evaluate the influence of mental disorders, often considered as reasons for idiopathic infertility, on female and male fertility, including stress, depression, sleep and eating disorders, and addictions.

Methods: This systematic review comprised a search of MEDLINE, Cochrane and PubMed databases for relevant articles that were analysed by two independent reviewers.

Results: A total of 106 articles published between 1955–2019 were included. Mental disorders modify endocrine gland and immune system functioning at both the tissue and cellular level, and are negatively associated with female and male fertility.

Conclusion: Mental disorders may negatively impact female and male fertility. Further studies are required to explain the exact role and contribution of mental disorders to fertility.

Keywords

Mental disorders, stress, depression, sleep disorders, eating disorders, infertility, idiopathic infertility

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Introduction

Fertility may be defined as a capacity to conceive and thus to produce offspring.[1] In contrast, infertility is defined as a disease characterized by a failure to establish a

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clinical pregnancy after 12 months of regular and unprotected sexual intercourse. Infertility in females may be categorised as primary, concerning females who have never been pregnant, and secondary, concerning females who have previously been pregnant.[2]

The problem of infertility is estimated to concern approximately 8–12% of the global population,[3] with secondary infertility occurring more often than primary infertility.[4] Furthermore, infertility is found to occur more often in less developed countries.[5] Males are estimated to be responsible for 20–30% of infertility individually, and are co-responsible for half of all infertility cases.[6]

Factors that may be associated with decreased fertility include time of unwanted non-conception, age of the female partner and number of diseases impacting fertility.[2] In addition, more recent research indicates that fertility is also influenced by male partner's age.[7] Infertility may be caused by various diseases related only to males (e.g. testicular deficiency), only to females (e.g. polycystic ovary syndrome [PCOS], endometriosis, uterine fibroids, or premature ovarian insufficiency) or diseases that can concern either sex (e.g. systematic diseases, infections, hyperprolactinaemia, or hypogonadotropic hypogonadism).[2]

Very often, it is impossible to establish the precise cause of infertility, and such a disorder is defined as idiopathic infertility. Idiopathic infertility may be explained by the role of mental disorders, such as stress, depression, sleep disorders, eating disorders, and addictions. The relationship between mental disorders and human physiology was first described in detail and highlighted by Hans Hugo Selye in 1955,[8] who stated that the stressor acts on the target (the body or some part of it) directly and indirectly through the pituitary and the adrenal glands. The first mediator travels from the injured target area to the anterior pituitary resulting in discharging of adrenocorticotropic hormone (ACTH). ACTH alone, or in cooperation with other hormones, stimulates the adrenal cortex to discharge corticoids. Mineralocorticoids stimulate the proliferative ability and reactivity of connective tissue, thus enhancing the inflammatory potential.[8]

The aim of the present study was to systematically review the literature to analyse and evaluate the influence of mental disorders, such as stress, depression, sleep disorders, eating disorders, and addictions, on female and male fertility.

Materials and methods

This systematic review, based on analysis of available literature indexed in MEDLINE, Cochrane and PubMed databases, was conducted independently by two reviewers (FS and JK) between June 2019 and October 2019, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Keywords used during the search of titles and abstracts were the combinations of (infertility OR fertility) AND (depression OR stress OR mental disorders OR antidepressants OR sleep disorders OR sleep disturbances OR sleep deprivation OR insomnia OR eating disorders OR anorexia nervosa OR bulimia nervosa OR binge-eating disorder OR addictions OR substance addictions OR alcohol OR smoking OR marijuana OR behavioural addictions OR [cell- OR mobile- OR smart-phone addiction]). Abstracts written in English and relevant to the topic were selected during screening. Full-text articles were critically studied and analysed in detail.

Results

A total of 3 561 records were retrieved once duplicates had been removed, and following screening, 743 articles were assessed for

eligibility. A final sample of 106 articles published between 1955 and 2019 were chosen for inclusion into the review (Figure 1). [AQ1]

Depression and stress

Approximately 350 million people suffer from depression worldwide, and many of those affected receive no proper treatment, mainly due to a global shortage of psychiatrists, ineffective treatment, ineffective mental health care system and stigmatization.[9]

Often weeks or even months are needed to obtain a response to antidepressant treatment.[10] In addition, adverse effects such as withdrawal syndrome, sexual problems, weight gain, and addiction are common.[11]

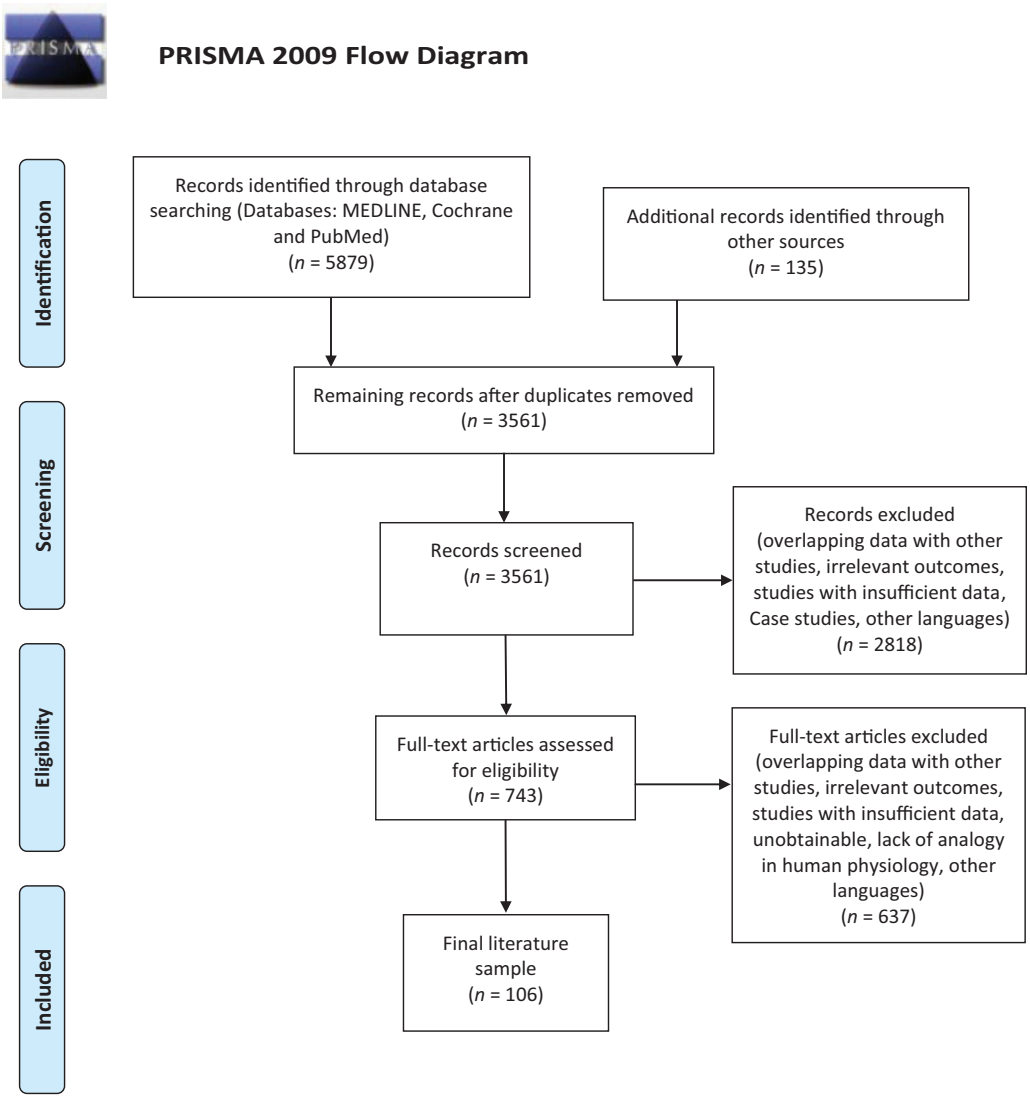

Figure 1. Flowchart of the studies identified in the systematic review.

Therefore, despite being more effective than placebo (odds ratios [ORs] of 1.15 to 1.55), antidepressants are associated with lower acceptability (ORs of 0.64 to 0.83).[12]

The problems of depression, stress, and anxiety significantly affect infertile people. A meta-analysis by Fallahzadeh et al.[13] showed that depression scores in women who are infertile were significantly higher than scores for fertile couples. Furthermore, a study by Crawford et al.[14] showed that women suffering from depression were less likely to undergo infertility treatment and more likely to be overweight or obese. Since biblical times, hypotheses have been raised about the relationship between depression, anxiety, and infertility. It is known that infertility may cause stress and even depression, but what remains unclear is whether depression, stress and anxiety affect fertility.[15]

Secretion of gonadotropin-releasing hormone (GnRH) pulses from the hypothalamus stimulates the pituitary gland to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[16] Both the amplitude and frequency of GnRH pulses are crucial for proper secretion of gonadotropins. LH secretion is stimulated by high frequency GnRH pulses, while low-frequency pulses stimulate FSH. During the follicular phase of the menstrual cycle, increased oestrogen levels lead to increased frequency of GnRH pulses. This results in increased LH secretion and ovulation. Many reproductive disorders in women are associated with abnormalities in GnRH secretion, and among others, this group includes hypogonadotropic hypogonadism, hyperprolactinaemia and PCOS.[17]

A study using a rat model of menopause and depression found that levels of cortisone, LH, FSH, and ACTH were significantly higher in groups subjected to mild stress factors compared with analogous groups not subjected to mild stress factors.[18] On the other hand, dopamine levels were lower in the stress groups.[18] While this is an interesting observation, similar effects have not been observed in humans. In addition, the effect of stress on the rat's fertility in this study is unknown, thus, the topic requires further research.

According to a study among women with recurrent miscarriages, as many as 45% showed anxiety and 37% had depressive symptoms, and these results were significantly higher than in women with low risk of miscarriage.[19] Furthermore, although major depression alone was not found to be associated with poorer results in female non-*in vitro* fertilization (IVF) fertility treatments, it lowered the chances of male partners to achieve conception.[20] Meanwhile, the use of antidepressants, particularly non-selective serotonin reuptake inhibitor (SSRI), has been found to increase the risk of first-trimester pregnancy loss.[20]

There are a number of published investigations regarding the influence of antidepressant drugs on fertility and miscarriages. In a Finnish cohort study of 6 920 women living in Vantaa, a correlation was found between the risk of miscarriage, antidepressant use, and body mass index (BMI).[21] Among women using antidepressants, the risk of miscarriage decreased as BMI increased. Women with low BMI who used antidepressants both before and during pregnancy were at the highest risk of miscarriage, and should be closely monitored to reduce the risk of preterm delivery.[21] In their work, Norr et al.[22] emphasized the negative impact of SSRIs on sperm parameters, particularly regarding dosage and duration of therapy. Spermatogenesis lasts at least 74 days, so at the beginning of therapy, sperm parameters may remain at their initial levels.[22] A study using a mouse model showed that sperm parameters are weakened by amitriptyline, but increased by venlafaxine.[23]

At the same time, the study showed that amitriptyline combined with vitamin C reduces the negative effect of amitriptyline on sperm motility.[23] Depression may be associated with an increased risk of premature ejaculation.[24] A meta-analysis by Yi et al.[25] showed that sertraline increases intravaginal ejaculation latency time and may be used for the treatment of premature ejaculation.

Depression, stress, and anxiety associated with infertility treatment are important issues. A study involving 842 patients undergoing IVF treatment showed that 39.4% of patients felt anxious, and 28.5% had depressive symptoms.[26] Another study found a relationship between the duration of infertility and the incidence of depressive symptoms and anxiety, whereby symptoms were most common in the group of patients suffering from infertility for 4–6 years.[27] A prospective cohort study of 72 patients treated with IVF showed that their salivary cortisol levels were higher than among the general female population. In addition, the highest levels were reached in a group undergoing IVF treatment for the first time. For this reason, relaxation techniques should be considered, especially during initial treatment.[28]

Depression, anxiety, stress, and antidepressants used in a patient's treatment can play an essential role in the treatment of infertility. The impact of these factors on hormonal balance, ovulation, miscarriages in women, as well as on the quality of sperm and ejaculation disorders in men, should be taken into consideration. In the present authors' view, patients' reproductive plans should play a role in determining the most effective therapy, while minimizing side effects. It is worth noting that infertility may be the cause of many cases of stress, anxiety or depression. Furthermore, in such situations, successful infertility treatment may have a positive impact on mental health.

Sleep disturbances and infertility

Sleep disturbances are commonly known to be associated with a number of diseases concerning the cardiovascular, endocrine, and nervous systems.[29] [AQ2] Furthermore, recent studies have shown that there is a relationship between sleep disturbances and reproductive health, which inevitably results in infertility.[30]

Polycystic ovary syndrome is characterized by hyperandrogenism, insulin resistance and oligoanovulation, and constitutes one of the most common endocrine system diseases among women of childbearing age.[31] PCOS also reduces fertility and is a common cause of female infertility.[30] Vgontzas et al.[32] reported that women with PCOS were 30 times more likely to suffer from sleep disordered breathing than women without PCOS, and a separate study demonstrated a correlation between obstructive sleep apnoea (OSA) and PCOS, in that 44.4% of women with PCOS experience OSA compared with only 5.5% of women without PCOS.[33] OSA is linked to increased reactive oxygen/nitrogen species and oxidative stress,[34] and oxidative stress is a recognized factor in both female and male infertility.[35,36] Further studies are needed to explain the exact role and contribution of OSA to the metabolic abnormalities in PCOS.[37] Moreover, patients with OSA are often characterized by hyperprolactinaemia that may indicate reproductive dysfunction in both sexes, resulting in infertility.[38] Effective continuous positive airway pressure therapy has been shown to decrease previously elevated serum prolactin levels in patients with OSA,[39] however, this study was limited by a relatively small male only study population.

Sleep disturbances coexist with circadian dysrhythmia and hypothalamic-pituitary-adrenal axis activation, and these factors directly or indirectly affect the inflammatory response, melatonin level, the level of reproductive hormones, and uterine

receptivity. All of these previously mentioned factors have a significant impact on infertility.[30] Hypothalamic-pituitary-adrenal axis activation affects reproductive hormone levels, and results in disorders of follicle development and menstruation, finally leading to infertility.[40–42] This phenomenon may be explained by a high level of ACTH and cortisol (stress hormone),[43] and such a situation is particularly intensified in the case of chronic insomnia.[30]

Despite the fact that melatonin is primarily related to circadian function, it is also thought to affect the reproductive system.[44] The exact role of melatonin in infertility is not entirely understood, but melatonin has significant antioxidant properties and protects the oocyte from oxidative stress, particularly at the time of ovulation.[45,46] In a study involving night-shift workers, melatonin levels were shown to be lowered, whereas LH and FSH levels were increased.[47] On the other hand, there is evidence that high melatonin level is associated with amenorrhea, hyperprolactinaemia, hypogonadotropic hypogonadism, especially among men with oligospermia and/or azoospermia.[48–51] Melatonin administration has been shown to enhance LH and FSH, possibly through GnRH during the follicular phase, but not the luteal phase, indicating that the effect of melatonin on reproductive hormones may vary depending on the cycle phase.[52] To summarize, both stable circadian rhythms and cyclic melatonin availability are critical for optimal ovarian physiology and placental function, however, further studies are needed to explain the exact role and contribution of melatonin to fertility.[46]

A high level of thyroid stimulating hormone (TSH) is responsible for anovulation, amenorrhea and recurrent miscarriages. Moreover, high TSH levels cause hyperprolactinaemia, which, as mentioned previously, is responsible for infertility in both partners.[53,54] During partial sleep deprivation, TSH concentrations have been shown to increase significantly and remain elevated throughout the following day.[55] Furthermore, Gary et al.[56] showed that TSH concentrations increased significantly as a result of total sleep deprivation, however, TSH concentrations were reduced during the second sleep deprived night compared to the first night, probably as a result of negative feedback inhibition. While sleep disorders are not a primary cause of hypo- and hyperthyroidism, there is evidence that sleep disorders may affect TSH level.

Levels of LH and FSH that are too high or too low may cause infertility.[57] Short periods of sleep time may result in a low FSH level and in consequence, in luteal phase dysfunction, and partial and total sleep deprivation could result in an increased LH amplitude.[30]

High androgen levels, particularly in women, are associated with PCOS and thus, with infertility.[58] Women with higher testosterone levels have been shown to have less sleep discontinuity.[59] For men, longer sleep duration results in higher testosterone levels.[30] Sleep loss in the early part of the night does not affect testosterone, while early wakening and wakefulness during the second part of the night has been associated with reduced morning circulating testosterone.[60]

Irregular oestradiol secretion may result in infertility. Partial sleep deprivation may increase oestradiol level, whereas variable sleep schedules would result in diminished levels. Low progesterone level has been correlated with infertility, and sleep-disordered breathing and stress are associated with a low level of progesterone.[30]

Furthermore, low sleep quality, sleep loss and interrupted sleep cause an inflammatory response in the form of elevation of tumour necrosis factors (TNF), interleukin (IL)-6, and C-reactive protein,[61,62] and all of these factors are correlated with unexplained infertility.[63,64] TNF-α is a central

regulator of inflammation that is associated with inflammatory mechanisms related to implantation, placentation, and pregnancy outcome. Obstetric complications related to the overproduction of TNF-α include recurrent pregnancy loss, early and severe pre-eclampsia, and recurrent implantation failure syndrome.[65] Furthermore, TNF-α has been shown to be significantly higher in infertile men with reduced sperm motility compared with fertile men.[66] IL-6 is a multifunctional cytokine with a crucial role in the inflammatory response, and is associated with embryo implantation and placental development, as well as the immune adaptations required to tolerate pregnancy.[67] Increased IL-6 level is associated with idiopathic infertility, recurrent miscarriage, pre-eclampsia, and preterm delivery.[64,67] An inflammatory state indicated by increased C-reactive protein level is positively correlated with adiposity and inversely correlated with pregnancy rates in women undergoing IVF. Furthermore, inflammation itself may suppress ovarian function, or indicate immune challenges that lead to ovarian suppression.[68–70]

Eating disorders

Anorexia nervosa is a severe psychiatric disorder characterized by extreme dissatisfaction with the size and/or shape of the patient's body or body parts that finally leads to weight phobia and food aversion. Desired (very low) body weight is achieved thanks to a strict diet and/or excessive hyperactivity.[71] Amenorrhea is estimated to occur in about 75% of women with anorexia nervosa, and oligomenorrhea is estimated to occur in about 8%.[72–74] Anorexia nervosa is associated with low BMI levels, low caloric intake, and excessive hyperactivity.[73] Menstrual cycle disturbances may be explained by a decrease in the leptin level and thus disruption of the pulsatile release of GnRH by the hypothalamus. Furthermore, in addition to regulation of GnRH secretion, leptin also affects LH level.[75,76] All of these factors would result in ovulation disruption and hypogonadotropic hypogonadism, and in consequence, would affect fertility. Moreover, decreased sexual desire and increased sexual anxiety is associated with anorexia nervosa,[77] and anorexia nervosa is also associated with an increased number of miscarriages and induced abortions.[78]

Like anorexia nervosa, bulimia nervosa is characterized by dissatisfaction with size and/or shape of body/body parts that finally leads to weight phobia and food aversion. However, in bulimia nervosa, a strict low-calorie diet is repeatedly interrupted by binge-eating episodes proceeding to feelings of losing control.[71] These episodes are followed by a variety of procedures to counteract the food ingestion, including vomiting, starvation, and laxative misuse.[79] Amenorrhea is reported in about 23% of patients with bulimia nervosa, whereas oligomenorrhea occurs in up to half of all bulimia nervosa cases.[72,73] Moreover, there is evidence that among patients with bulimia nervosa and oligomenorrhea, the LH and FSH levels are pathologically low.[80] PCOS was mentioned previously to diminish fertility, and it is also associated with bulimia nervosa. In fact, 76% of patients with bulimia nervosa are shown to have PCOS.[81]

Binge-Eating Disorder (BED) is characterized by binge-eating episodes proceeding to feelings of losing control, similar to bulimia nervosa. However, BED is not associated with a variety of procedures to counteract the food ingestion.[71] As in the case of anorexia nervosa and bulimia nervosa, patients with BED also experience oligomenorrhea and amenorrhea.[82] Moreover, there is evidence that binging leads to insulin increase. High insulin levels cause an increase in testosterone levels, which negatively affects fertility.[83] What is more,

similar to anorexia nervosa and bulimia nervosa, BED is associated with PCOS.[73] BED is also associated with an elevated risk of miscarriages and worse sexual functioning compared with patients without BED who are obese.[78] Furthermore, obesity, as one sign of BED, is a significant risk factor for endometrial cancer, and endometrial cancer treatment methods may lead to infertility.[84]

Addictions

Substance addiction is a neuropsychiatric disorder characterized by a recurring desire to continue taking the substance despite harmful consequences.[85] It has a direct impact on fertility, primarily through the harmful effects of misused substances.

In the case of women, acute alcohol consumption may increase oestrogen levels leading to a decrease in FSH, finally resulting in ovulation disorders.[86] What is more, alcohol intake has a negative effect on semen volume and semen morphology, and reduces testosterone level among males, and differences in these factors were more significant when comparing daily versus occasional alcohol consumers, rather than occasional versus non-consumers.[87]

Published literature emphasizes an association between cigarette smoking and infertility. The prevalence of infertility and time to conception is higher, whereas fecundity is lower, among smokers compared with non-smokers,[88] and FSH levels are elevated among active and passive smokers compared with non-smokers.[89] Moreover, urinary oestrogen excretion is lower among smokers, and smoking females may experience earlier menopause.[90] What is more, among smoking females, there is an increased risk of spontaneous miscarriages.[91] Smoking males have demonstrated a reduction in sperm density, motility and pathologies in sperm morphology.[92]

Women who smoke marijuana demonstrate increased serum testosterone levels, decreased prolactin secretion and suppressed or increased serum LH level in a menstrual stage-specific manner,[93] all of which would result in menstrual cycle disorders with significant effects on fertility. Furthermore, female marijuana smokers undergoing *in-vitro* fertilization demonstrate poor oocyte retrieval rates.[94] In the case of males, marijuana smoking may cause a reduction in the volume and number of spermatozoa and may cause morphology changes, which results in sperm hyperactivity and reduction of fertilization capacity.[95]

Mobile phone overuse (behavioural addiction) has been suggested to decrease sperm parameters (count, motility, viability, and morphology) and increase oxidative stress, however, the effects appear to be the result of emitted radiofrequency electromagnetic waves.[96,97] Direct effects of other behavioural addictions on human fertility have not been proven. However, social media addiction, video game addiction, gambling problems, internet addiction, and exercise addiction are associated with depression, which is an infertility risk factor described previously in the current paper.[98–101]

It is worth noting that substance addiction is much more common in people suffering from eating disorders than in the general population. In addition, more than one-third of people with substance addiction report eating disorders.[102,103]

Furthermore, addictions are often associated with risky sexual behaviour, such as frequently changing sexual partners or unprotected sex with an unknown person.[104] This leads to an increased risk of contracting sexually transmitted diseases which, if left untreated, are responsible for most cases of tubal factor infertility.[105,106]

Conclusion

An analysis of the literature carried out during the present systematic review highlights the negative impact of mental

disorders, such as stress, depression, sleep disorders, eating disorders, and addictions on female and male fertility. These disorders modify the functioning of endocrine glands and the immune system at both the tissue and cellular level, all of which may result in reduced fertility.

Despite these associations, it is not entirely clear to what extent mental disorders affect fertility and to what extent infertility affects mental health. Further studies are certainly required in order to explain the exact role of mental disorders in fertility and the contribution they have to infertility. Furthermore, a comprehensive approach to the diagnosis and treatment of infertility is critically needed, that includes analysis of the mental state of the couple desiring a child, in order to significantly reduce the number of idiopathic infertility diagnoses.

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