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REVIEW

The role of physical agents' exposure in male infertility: A critical review

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Summary *Background: A decrease in semen quality is an increasingly widespread pathological condition worldwide. Jobs and lifestyles have changed a lot with the advancement of technology in the last few decades, and a new series of risk factors for male infertility have spread.*
Objective: This review aims to summarize the current literature on this relationship, evaluating alterations in semen parameters and hormonal profile.
Methods: A deep research was performed through MEDLINE via PubMed, Scopus, and Web of Science on articles regarding the relationship between physical agents and male fertility over the last twenty years. Some physical agents already associated with male infertility, such as heat and radiation, while emerging ones, such as physical exertion, psychological stress and sedentary activities, were newly considered.
Results: Most studies described sperm quality after exposure. Overall sperm impairment was shown after radiation and alteration of specific parameters, such as sperm concentration, were observed after psychological stress and sedentary work. In addition, an association was also reported between physical exertion and hormonal profile, especially pituitary hormones and testosterone.
Conclusions: Although the associations between physical agents and male infertility are suggestive, the level of evidence of the studies is not adequate to define their influence, except for physical exertion. Therefore, new prospective studies are necessary for the validation of the correlation and the possible safeguarding of the exposed working classes.

KEY WORDS: Male fertility; Semen parameters; Hormonal profile; Physical agents.

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INTRODUCTION

According to WHO, infertility is a disease of the reproductive system defined by the inability to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. This dysfunction affects up to 15 % of couples, and the cause of over 1/3 of them is male infertility (1). It affects 60-80 million couples over the world (2), and the decline in semen quality occurred over the past century, concomitant to an increase in genitourinary abnormalities (such as cryptorchidism, testicular carcinoma, and hypospadias) (3).
The percentage of male infertility ranges from 2 to 12%, with the highest rates in Africa and Central/Eastern Europe and 20-70% of inability to conceive in those areas is attributable to the male gender (4). However, these percentages are not veracious due to an underestimation given by a low number of populations involved, the non-unique clinical definition of infertility and religious and cultural restrictions. Furthermore, the effect of COVID-19 infection on semen quality still needs to be verified, although mechanisms of testicular damage have been reported (5).
This clinical condition depends on different underlying pathologies, which include anorchia (vanishing testis syndrome, Swyer syndrome), sperm production dysfunction or obstruction from ejaculatory ducts to seminal colliculi. In particular, spermatozoa dysgenesis could be determined mostly by exogenous factors. Indeed, environmental factors seem to influence semen quality aberration. Several articles showed the impact of the environment on male infertility (6, 7), with various incidences according to the considered population (8). In a recent review, *Benatta et al.* reported a strict correlation between nutrition and male infertily, especially due to the industrialized mass food production and the subsequent ingestion of xenobiotics (9). Although the association between exposure to chemicals, such as pesticides (10), is supported, some doubts remain about the physical ones (11). Therefore, this narrative review aims to discuss the main work-related male fertility risk factors.

MATERIALS AND METHODS

Search design

We conducted a comprehensive literature search on studies discussing physical risk factors for male fertility, between April 4 and May 6, 2022, consulting PubMed and Scopus. The following keywords were used: male infertility, male impairment, DNA damage, human sperm, semen parameters, and genotoxicity. They were associated with the most discussed risk factors, such as heat, physical exertion, radiation, sedentary work, and psychological stress.

Identification of studies

We considered the observational studies, published after the 2000s, describing the correlation between physical agents' exposure and male infertility. We evaluated the papers according to the *Patient Intervention Comparison Outcome Studytype* (PICOS) model. P: general population or workers; I: exposure to heat, physical exertion, radiation, sedentary work, or psychological stress; C: comparison with healthy non-exposed male volunteers; O: semen parameters (ejaculate volume, sperm count, sperm concentration, total sperm motility, and sperm morphology) or sex hormone [*follicle-stimulating hormone* (FSH), *luteinizing hormone* (LH) and *Testosterone hormone* (TH)] levels or DNA fragmentation; S: observational studies.

Eligibility criteria

All published human articles in English have been reviewed. The evidence cited in this review comes only from human selected based on the following criteria:

- Exposure to the risk factor was occupational or environmental.
- Assessment of semen quality, histological examination, or sperm cells DNA fragmentation.
- Evaluation of sex hormone profile and hypothalamic-pituitary-gonadal (HPG) axis status.

Articles relating only to epidemiological investigations, sex chromosome ratio or other systems were excluded. The quality of all included studies was estabilished the Newcastle-Ottawa-Scale and evaluation forms.

Results

PRISMA flow diagram of the study was reported in Figure 1. Eight hundred and fifty-six (856) studies published were identified. Two independent authors screened all retrieved records. Seven hundred and seventy six (776) articles were excluded by the title and abstract reviewing. Eighty (80) were assessed for full-text eligibility. Fourty-four (44) studies were excluded due to the following resons: 38 articles regarded chemical agents' exposure, and 6 were studies on the sperm sex chromosome ratio.

The 36 remaining studies were divided according to the agent considered:

- 4 for heat exposure.
- 9 for physical exertion.
- 12 for radiaton.
- 5 for sedentary work.
- 6 for psychological stress.

Heat

In case of heating of the testicles, an increased metabolism without a corresponding increase in blood supply may occur, with subsequent local hypoxia and harmful effect on spermatozoa. In addition to idiopathic diseases, exogenous factors, such as lifestyle and work, may contribute to a higher temperature of the testicle (12).

This risk factor encompasses many types of jobs in both developing and industrial countries. *Bakers* in *Saudi Arabia*, exposed to a *wet-bulb globe temperature* (WBGT) of 37°C, had an infertility rate of 22.7% compared to 3% of the healthy volunteers (13). In a cohort study of the steel industry (workers undergoing WBGT of 36°C) there was a statistically significant difference in seminal parameters (semen volume, sperm morphology, motility, and count) compared to the a non-exposed group (14). Nevertheless, *Shef et al.* reported the reversible toxic effect of hyperthermia on semen quality after cessation of heat exposure (15). However, there is not always a significant reduction in semen quality also for workers exposed to extreme heat (16).

All considered studies about heat exposure are summarized in Table 1.

Physical exertion

Moderate physical activity (PA), in addition to better health and decreased stress, contributes substantially to increasing the chances of couples seeking pregnancy. However, an excessive intensity of the exercises may cause stress with an attached alteration of fertility.

Experimental human studies confirmed inflammatory pathogenesis. A *Reactive Oxygen Species* (ROS) and seminal cytokines increase during aerobic and nonaerobic isomet-

Figure 1.

PRISMA 2009 flow diagram.

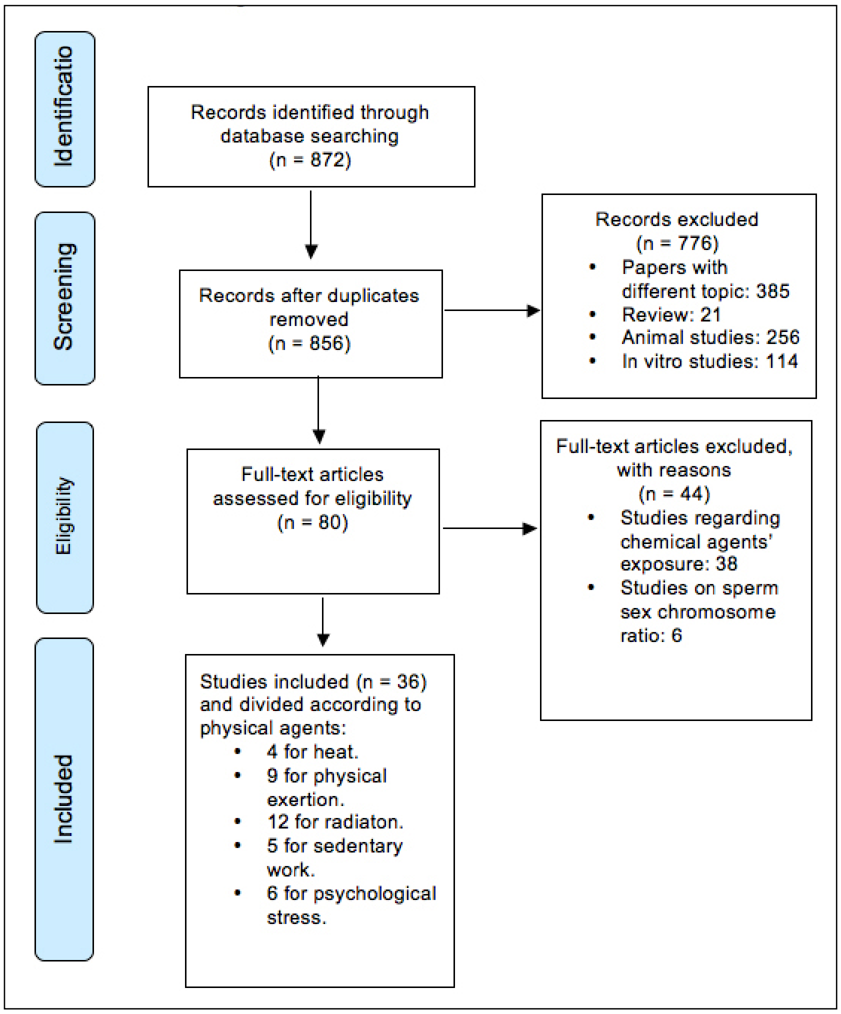

Table 1.
Studies concerning the effects of heat on male fertility.

Reference	Type of clinical study	Examined population, n	Reproductive effects
Al-Otaibi (12)	Cross-sectional study	137 Bakers	Infertility rate of 22.7% *vs* 3% in control group
Hamerezaee et al. (13)	Cross-sectional study Cohort study	30 steel industry workers exposed to heat; 14 workers not exposed	Significant reduction in sperm volume, normal morphology, motility, and count
Shefi et al. (14)	Cross-sectional study	11 infertile men after known hyperthermic exposure.	Sperm quality impairment improved after the termination of the exposure
Eisenberg et al. (15)	Cross-sectional study Cohort study	98 Workers exposed to extreme heat, 358 workes exposed	Work not associated with semen quality

Table 2.
Studies concerning the effects of physical exertion on male fertility.

Reference	Type of clinical study	Examined population, n	Exercise period	Reproductive effects
Hajizadeh Maleki et al. (16)	Clinical trial	24 long-distance road cyclists	16 weeks	Low Semen volume,sperm motility, normal morphology, concentration, and count
Pelliccione et al. (17)	Clinical trial	7 experienced mountaineers	10 days	Reduction of sperm concentration, increase in serum Testosterone
Verratti et al. (18)	Clinical trial	7 mountain climbers	5 days	Reduction of sperm forward motility, increase in LH
Safarinejad et al. (19)	Randomized controlled trial	143 subjects assigned to high-intensity exercise, 286 to moderate-intensity exercis	60 weeks	Reduction of sperm count, concentration and motility and LH, FSH and Testosterone. Higher changes in high-intensity exercise than moderate - one. Regular parameters after recovery period
Vaamonde et al. (20)	Randomized controlled trial	8 non-professional athletes, 8 controls	Short-term exhaustive endurance exercise, 2 weeks	Reduction of LH and FSH. changes in volume, sperm concentration, count, type "a" and "d" velocity, and moprhology
Mínguez-Alarcón et al. (21)	Cross-sectional study	215 healthy young men	-	No significative differences.
Gebreegziabher et al. (26)	Cross-sectional study	10 long distance competitive cyclists, 10 volunteers performing minimal or no exercise	-	Reduction of sperm normal morphology
Tartibian et al. (27)	Cross-sectional study	56 elite athletes, 52 physically active volunteer men	-	Lower semen volume, motility, sperm count and normal morphology. Higher MDA and ROS levels and DNA fragmentation rate
Eisenberg et al. (28)	Cross-sectional study	145 men doing strenous work, 311 controls	-	Lower semen concentration and total sperm count

ric exercise was reported, as demonstrated by malondialdehyde (a marker of lipid peroxidation), lipid hydroperoxide and carbonyls, regardless of concomitants augmented levels of *superoxide dismutase* (SOD), catalase, and total antioxidant capacity (17-19). Besides, semen impairment is associated with an altitude greater than 2000 m and the consequent risk of hypoxia among mountaineers (20, 21). HPG axis is also involved, with the reduction of *Gonadotropin-Releasing Hormone* (GnRH) and production of inhibin (with consequent decrease of FSH, LH, total and free TH and increase of Prolactin) (22, 23).
It is noteworthy that the complete recovery of fertility occurs at different times according to exposure and age (18). On the other hand, *Mínguez-Alarcón et al.* found in their study that there are no significant differences in semen at different intensities of exercise (24).
Physical effort occurs in various jobs, from professional athletes to manual workers. As for the first category, in the rugby and soccer players, both SOD and neutrophil levels were higher after a match and the entire season (25, 26). Furthermore, the cyclists have a lower proportion of spermatozoa with normal morphology (27), while there is also an impairment in volume, motility, count and DNA fragmentation in contact sports (28). The strenuous work negatively impacts the mean sperm count and concentration more than other work-related risk factors (29).
Studies are shown in Table 2 and reported an unequivocal association between physical effort and male impairment.

Radiation

Radiation is one of the most in-depth topics considering pathogenesis and its effects on men, as shown in Table 3. The only experimental study was conducted on some prisoners: spermatocytes and spermatids can be damaged, respectively, at 2-3 Gy and 4-6 Gy, and infertility becomes permanent at 3-5 Gy; furthermore, complete recovery can be obtained at 9-18 months if < 1 Gy and 5-years or more with a dose of 4-6 Gy (30). Nowadays, only observational studies occur for obvious ethical reasons.
Human studies can be divided according to whether the exposure was to not ionizing or ionizing radiation.
The former includes low-frequency energies on the electromagnetic spectrum, including radiofrequency, microwaves, infrared and ultraviolet radiations. Several routinely used sources emit them, such as mobile phones, which have a wide range of SAR. In a study examining 371 male volunteers, the proportion of rapid progressive motile sperm was significantly lower in men who used their phone for over 60 minutes/day (31). As well, *Agarwal et al.*, dividing men according to their active cell phone use, reported a linear relationship between its use and the decrease in total sperm count, motility, viability, and normal morphology (32). Not ionizing radiation exposure occurs in several jobs. Telecommunications and sonar/radar operators have an increased risk of infertility (OR = 1.72 and OR = 2.28, respectively) (33). Even men in the Royal Norwegian Navy had a higher risk of infertility due to radiofrequency electromagnetic fields exposure, especially in men closer than 10 m from highfrequency aerials (OR = 1.93) (34).
Ionizing radiation comprehends all high energy waves, including alpha, beta, and gamma rays, and removes electrons from atoms and molecules of materials. *Wdowiak et al.* proved that natural and artificial Alfa, Beta, and Gamma radioactive isotopes do not affect semen volume, count, density, and motility, but viability is negatively related to the Gamma isotope, and the percentage of sperm with nor-

Table 3.
Studies concerning the effects of radiation on male fertility.

Reference	Type of clinical study	Examined population, n	Radiation type	Reproductive effects
Fejes et al. (30)	Cohort study	371 male volunteers: 59 high transmitters (use over 60 minutes/day), 195 control group 1; 88 humans keeping cell phone in the standby position for more than 20 hours daily, 106 control group 2	Not ionizing	High transmitters had a decrease in the proportion of rapid progressive motile sperm and an increase in slow progressive motile sperm. No differences in sperm based on duration of standby
Agarwal et al. (31)	Cross-sectional study	361 humans divided according to their active cell phone use: group A: no use (40); group B: 4 h/day (107); group C: 2-4 h/day (100) and group D: > 4 h/day (114)	Not ionizing	Decrease in sperm count, motility, viability, and normal morphology with the increase in daily use of cell phone
Møllerløkken et al. (32)	Cross-sectional study	1.487 Norwegian Navy personnel	Not ionizing	Telecommunications and sonar/radar operators have an OR of 1.72 and 2.28 respectively
Baste et al. (33)	Cross-sectional study	10.497 currently and formerly employed military men	Not ionizing	Nearness to high frequency aerials is positively related to higher risk of infertility. OR for low degree is 1.39 and OR for high degree is 1.93
Wdowiak et al. (34)	Cross-sectional study	4.250 patients attending at fertility center and spermiogram was rrelated to background radioactivity in the Lublin region	Ionizing	Sperm viability is negatively associated with the Gamma isotope, and normal morphology is negatively related to Beta and Gamma ones
Green et al. (35)	Cross-sectional study	6.224 adult survivors of childhood tumor	Ionizing	Reduced or almost compromise ability to siring a pregnancy
Gandini et al. (36)	Cross-sectional study	166 patients affected by testicular cancer, 95 underwent to radiotherapy, 71 underwent to chemiothgerapy	Ionizing	Decrease in ejaculate volume, sperm concentration, count and normal morphology. Greater ricovery in subgroup exposed to < 26 Gy for sperm conenctration and count
Bezold et al. (37)	Cross-sectional study	7 male soldiers	Ionizing	In 57% complete azoospermia, associated with increase in FSH and LH, and in 14% severe oligozoospermia
Kumar et al. (38)	Cross-sectional study	83 workers occupationally exposed to ionizing radiation and 51 non-exposed control	Ionizing	Decrease in sperm motility, viability, and morphological abnormalities; increase in DNA fragmentation and sperm head vacuoles
Kumar et al. (39)	Cross-sectional study	83 workers occupationally exposed to ionizing radiation and 51 non-exposed controls	Ionizing	Higher DNA fragmentation in exposed men
Andreassi et al. (40)	Cross-sectional study	31 interventional cardiologists; 31 clinical cardiologists	Ionizing	Increase in micronuclei (MNs), derived from acentric chromosome fragments or whole chromosomes, and it positively related to years of work
Doyle et al. (41)	Cross-sectional study	5.353 employers in nuclear industry	Ionizing	No evidence of association between exposure to low level ionising radiation among men with primary infertility

mal morphology is negatively associated with to Beta and Gamma ones (35). Radiation therapy is also a dangerous risk factor, affecting every age range. Over the threshold value of 7.5 Gy, adult survivors of childhood tumours have a reduced or almost compromised ability to siring a pregnancy and more chances of becoming oligospermic than those not exposed (36). After 1-year of Radiotherapy in adults, all semen parameters are significantly lower (37). Even among all Georgian soldiers, the exposure to Cesium-137 caused complete azoospermia or critical alterations of semen morphology and motility (38). In diagnostic radiation systems, sperm motility ($p < 0.001$), viability ($p < 0.05$), and normal morphology ($p < 0.001$) were lower in exposed personnel than in healthy men (39). Furthermore, *Kumar et al.* discovered that sperm DNA denaturation is significantly higher ($p < 0.0001$) and associated with higher total seminal plasma glutathione (GSH) ($p < 0.01$) and Total antioxidant concentration ($p < 0.001$) in seminal plasma always in health workers occupationally exposed to radiation than control (40). An increase in micronuclei (MNs) derived from acentric chromosome fragments (or whole chromosomes) was also reported among interventional cardiologists ($p = 0.02$), with a subsequent higher levels of somatic DNA damage (41).

Nevertheless, in a study on employees of the nuclear industries, there was no evidence of an increase in the incidence of infertility compared to the population, even though the median received radiation dose was 12.3 mSv (42).

Sedentary work

Sedentary activity (SA) occurs in several occupations, such as doctors, engineers, administrators, car drivers, and office workers Studies on men show that this risk factor is negatively related to sperm count and concentration (43) and TH (44). As mentioned before, the scrotal temperature is closely associated and increases in these conditions with an average value of 0.7°C higher, even 1.7-2.2°C in car drivers (45), with an attached reduction in sperm count (46). Hjollund also discovered that sperm concentration decreased by 40% for every 1°C increase, and Inhibin B levels decreased in men with the highest daytime scrotal temperature (47).

However, in another study, there are no statistically significant differences in semen parameters, although those who spend more than 50% of the seated work time have a higher *DNA fragmentation index* (DFI) (48).

Although there is proven evidence of heat stress induced by prolonged sitting in Table 4, further investigation is needed to demonstrate sedentary work as a risk factor or whether it requires a sedentary lifestyle.

Psychological stress

The distribution varies according to gender, geography, and technological progress, with greater frequency in women, inhabitants in Europe and cities than men, those in Asia and rural environments, respectively (49, 50).

Men were analysed in different contexts, with several stressors. In a cross-sectional study, the stress levels in the general population according to a questionnaire were inversely proportional to the values of the semen parameters, affecting sperm count, volume, and concentration (51). *Eskiocak et al.* evaluated the university students, noting

Table 4.
Studies concerning the effects of Sedentary work on male fertility.

Reference	Type of clinical study	Examined population, n	Reproductive effects
Gaskins et al. [42]	Cross-sectional study	189 healthy young men	Sperm concentration and count were inversely related to sedentary activity. OR of 5.45 of low sperm concentration in less active men compared to active men
Priskorn et al. [43]	Cross-sectional study	1210 healthy young men	Time spent watching television was associated with lower sperm counts, an increase in follicle-stimulating hormone and decreases in testosterone
Hjollund et al. [45]	Cross-sectional study	60 men doing sedentary work	Elevation in scrotal skin temperature is associated with a substantially reduced sperm concentration
Hjollund et al. [46]	Cross-sectional study	99 healthy men	Decrease in Sperm concentration, count, FSH per 1°C increment of median daytime scrotal temperature
Gill et al. [47]	Cross-sectional study	152 men who spent ≥ 50% of their time at work in a sedentary position; 102 men who spent < 50% of their time	No statistically significant differences in semen parameters although who spend more than 50% of the seated work time have a higher DFI

Table 5.
Studies concerning the effects of psychological stress on male fertility.

Reference	Type of clinical study	Examined population, n	Reproductive effects
Nordkap et al. [50]	Cross-sectional study	1215 young men	Sperm count, volume and concentration inversely related to stress
Eskiocak et al. [51]	Cross-sectional study	27 university students	Sperm concentration, total and rapid progressive motility reduction
Gollenberg et al. [52]	Cross-sectional study	744 healthy men	Men reporting 2 or more recent stressful life events had reduced sperm concentration, motility and morphology than < 2
Boivin et al. [53]	Cohort study	818 males in Fertility clinics	More marital distress required more treatment cycles to conceive (OR = 1,20)
Zou et al. [54]	Cross-sectional study	384 adult male workers, 88 with high work stress and 296 with low stress	Decrease in sperm concentration and or total sperm count in stressed workers
Janevic et al. [55]	Cross-sectional study	193 healthy men	Inverse association between perceived stress score and sperm concentration, motility, and normal morphology

lower levels of sperm concentration, total and rapid progressive motility, and arginase activity before their exams, associated with increased *nitrogen monoxide* (NO) and *superoxide dismutase* (SOD) (52) in seminal plasma. The most frequently encountered stressor in studies is the visit to infertility clinics: an alteration in sperm concentration and motility (53), normal morphology was reported, with a negative association between the degree of stress and the ability to sire a pregnancy (54).

Psychological stress also affects the work environment, influencing some of them heavily. Consulting responses from the Job Content Questionnaire, reduced sperm concentration and count values were detected (55), and men who experienced two or more stressful life events in the past year had a lower percentage of motile sperm and a lower percentage of morphologically normal sperm (56). Cited studies, summarised in Table 5, demonstrate the validity of psychological stress as an influencing agent for male impairment.

Discussion

This paper reviewed the literature that investigated the impact of physical agents on male fertility. Some agents with a known influence on male fertility have been considered, such as Heat and Radiation, likewise emerging ones, such as Physical Exertion and Psychological stress.

Heat

An optimal test temperature of 3°C lower than in arterial circulation is necessary for spermatogenesis (57). This process is ensured by a cooling process involving the scrotum, pampiniform plexus, and muscles due to the heat exchange mechanism between incoming arterial blood and outgoing venous blood (58). A correlation between testis heat and spermatogenesis occurs, as demonstrated by the latter improvement in patients undergoing after operation for varicocele (59). The environmental temperature also plays a role in fertility as it is inversely proportional to total sperm number, non-progressive motility, and normal morphology (60). In an extensive literature review from 1998, *Thonneau et al.* reported that sperm morphology was the semen parameter most affected with a concomitant increase in time to pregnancy (61). Many experimental studies on animals showed the activation of *heat shock protein* (HSP) by heat, with consequent DNA damage, formation of pyknotic nuclei, autophagy and, at least, apoptosis (62, 63). Various types of morphological and functional alterations in high-temperature environments have emerged. An experimental study on broiler breeders was carried out: the *sperm quality index* (SQI) of subjects with normal semen parameters had been reduced after exposure to constant high temperatures, concomitant with a higher percentage of dead sperm, while the heat stress does not cause further deterioration in cases with poor SQI (64). Always *Karaca et al.* showed that the SQI decreases after a mix of control sperm with the *seminal plasma* (SP) of cases exposed to T of 32°C, while the sperm of the exposed combined with the SP of healthy subjects determined lower levels of *Calcium* (Ca), with the consequent decrease in sperm motility, and lower fertility (65).

Only four papers on heat exposure were recently published. In two of them, alterations of several semen parameters were shown (such as sperm normal morphology, total motility, and count) (14, 15), and a higher rate of infertility was reported among bakers in another study

(13). Another remarkable element is the reversibility of this effect on semen quality. *Eisenberg et al.* showed that heat exposure in certain occupations, such as welders, is associated with altered semen quality, while other jobs have not demonstrated a detriment to semen production (16). Therefore, an adequate temperature and sufficient exposure time are necessary to reach a condition of irreversible semen impairment.

Physical exertion

Although physical activity is recommended for a healthy lifestyle. Indeed, an improvement of all semen parameters (primarily rapid progressive sperm motility) and a reduction of inflammation and oxidative stress markers occur after 3-6 months of training (66, 67). Physical exertion may be related to male infertility, and it may be secondary to the immune system due to the proinflammatory cytokines increasing during heavy exertion (68). These proteins are negatively related to sperm motility and morphology (69), and they increase the activity of lipid peroxidation in the sperm cell membrane and DNA damage in both mitochondrial and nuclear genomes (70) through a rise of ROS production (71). Higher antioxidants enzymes levels in athletes than in sedentary subjects occur (72, 73), although their synthesis in semen occurs mainly along the vas deferens, and, therefore, direct ROS damage to the testicles and no compensation for spermatogenesis are conceivable (74).
A comparison between triathletes and men who practice regular physical activity showed lower levels of sperm motility, morphology, and count (75); even cycling more than 5-h per week was associated with low sperm concentration (76). In a study on Extreme Mountain Bikers, abnormal findings in the scrotal US were reported in 94% of cases, including the most frequent scrotal calculi, epididymal cyst and epididymal calcifications, compared to 16% of controls (77). Furthermore, physically "*more active*" young men have a higher percentage of immotile sperm than "*less active*" subjects (78). In endurance-trained males, there is a significant reduction in resting *Testosterone hormone* (TH) after 6-months of intense training with attached altered prolactin and lutropin release (79).
In the majority of the considered studies, Physical Exertion was associated with altered semen parameters. The most frequent were sperm motility and concentration, although sperm
morphology, count, and semen volume were statistically different in most cases. Furthermore, controversies about the effect of physical exertion on the HPG axis have emerged. Only in 2 out of 4 studies evaluating the hormonal profile did a reduction in FSH, LH or testosterone occur. Nevertheless, considering the period of exercise, it appears that, in the first few days of training, there is an increase in sex hormones and a subsequent decline. The overall evidence level of the included studies is noticeable due to the many clinical trials present. Therefore, we can see a strong correlation between physical exertion and male infertility.

Radiation

Radiation is one of the most widespread physical agents, given its presence in the environment and the devices used routinely. The testis is one of the organs most sensitive to this risk factor because mature spermatozoa are unable to repair damage by radiofrequency (80), whose mechanism is entrusted to Sertoli cells through *non-homologous end joining* (NHEJ) (81). *Bergonié* reported that the less differentiated cells with higher reproductive activity are the most susceptible to x-rays (82). The sensitivity of spermatogenesis to radiation depends on the wavelength, the time and duration of the exposure, the higher number of non-differentiated cells, and the water content (the effect is directly proportional to the amount of water) (83). The amount of absorbed radiation depends on several factors, which influence the averaged whole-body *specific absorption rate* (SAR). Its threshold level is 1,6 W/Kg, as decreed by *Federal Communications Commission in the USA*, while Europe follow *International Electrotechnical Commission* guidelines, so it is 2 W/Kg (84).
The irradiation of the spermatids at 3.5-6 Gray can cause damage to the testis and may determine permanent infertility, with a risk of congenital anomalies to the offspring (85). Nevertheless, infertility can be transitional with 150 mSv (86) or 2-3 Gy and 4-6 Gy (with recovery times of 10-24 months and up to 10 years, respectively) (87). The long-lasting effect of radiation time depends on the foci of γH2AX formed after exposure (88); the repair occurs in two hours, but this period increases already in spermatocytes with exposure over 1 Gy (89).
DNA damage from *Electromagnetic fields* (EMF) is also secondary to ROS formation (90). Although their small dose can favour capacitation, the acrosomal reaction and the fusion with the oocyte (91, 92), oxidative stress reduces sperm count, motility, and viability, inducing lipid peroxidation, a decrease in sperm motility, DNA damage and apoptosis (93). Besides, it seems responsible for increased apoptosis and is involved in testicular carcinogenesis (94).
In the last in vivo experiments, three categories of topics have emerged:

1. Effects on sperm cells: after exposure, count, motility, normal morphology, and viability decreased considerably (95).
2. Spermatogonia radiosensitivity: sperm cells are less vulnerable than somatic ones due to the complex of the seminiferous tubules, but the repair mechanism to DNA damage is slower or not present (96, 97). Nevertheless, these considerations are not very relevant because the chromatin in the gametes of mice is more compact than humans and, therefore, less susceptible (98).
3. Involvement of HPG axis: *Wang et al.* found under electron microscopy that Leydig cells are more susceptible to radiation damage with reduced serum TH (99). The hypothalamic cells producing GnRH also seem to be affected (100), with a reduction in the circulation of FSH, LH and TH (101).

Most included articles showed a correlation between radiation and male infertility, considering several variables, such as semen parameters, DNA fragmentation index, and ability to siring a pregnancy. As for not ionizing radiation, both studies evaluating semen quality reported a decrease in sperm motility and viability, confirming a targeted action based on the concentration of superoxide anion in semen (102). Almost 15,000 military men were

recruited in the other two studies to assess the risks associated with radiofrequency electromagnetic fields. Proximity to a source that emits radiation is positively associated with the risk of male infertility, with an odds ratio ranging from 1.4 to 2.3 (33, 34).
Even ionizing radiation seems to harm semen parameters. Among patients with testicular cancer who underwent radiotherapy, male soldiers and workers occupationally exposed to ionizing radiation, an overall semen quality impairment occurs, especially for sperm normal morphology and total count. In the three studies assessing its effect on the cell nucleus, two reported a higher DFI value than controls, whereas the micronuclei frequency was higher among interventional cardiologists in the other one. Furthermore, adult survivors of childhood cancer have a reduced or almost compromised ability to siring a pregnancy (36). In summary, a negative impact of ionizing and non-ionizing radiation emerged, also focusing on children.

Sedentary work

In a period of technological development and consequently the use of computers and prolonged sitting, the sedentary occupation has become widespread and more frequently associated with other risk factors that may contribute to infertility, such as physical inactivity and obesity. The etiopathogenesis is related to high scrotal temperature following prolonged sitting, which may imply a reduction in sperm count and concentration (103).
Although several times they were used as synonyms in literature, *physical inactivity* (PI) is a different concept compared to a sedentary lifestyle since it means failure to reach the recommended PA threshold value (at least 150 minutes of moderate PA per week) (104). Even PI has a higher incidence in infertile men, with a decrease in almost all semen parameters (concentration, viability, motility, and morphology) and hormonal levels (FSH, LH and TH) (105, 106). Nevertheless, SA and PI frequently coexist and negatively affect male fertility.
In two controlled trials, where men had to practice moderate exercise regularly, there were evident reductions in inflammation and oxidative stress with the improvement of all semen parameters, DNA integrity, pregnancy rate and TH in obese people (107, 108).
In four out of the five articles sperm quality was affected and the most frequent were sperm concentration and total count (three out of four). In the two articles evaluating the hormonal profile, a reduction in FSH and TH occurred, respectively. However, *Gill et al.* reported no association between SA and semen quality alterations, although a higher DFI occurred in patients who spent ≥ 50% of their time at work in a sedentary position (48). Given the low number of papers and their evidence level, no definitive conclusions can be obtained; further studies are necessary to establish a substantial correlation between sedentary work and male infertility.

Psychological stress

In 1936 *Hans Selye* defined stress as the non-specific response of the organism to every request. This process consists of three distinct phases: Alarm, Resistance, and Exhaustion. In the first two steps, the subject uses his resources and therefore tries to adapt, while, in the last one, the defences fall, and physical, physiological, and emotional symptoms occur.
Hypothalamic-pituitary-adrenal (HPA) axis mediates the stress response. The paraventricular nucleus activates the catecholaminergic system and produces the hormone CRH, the starting point of the HPA axis, determining the production of glucocorticoids. The latter determines the suppression of the transcription of the GnRH receptor gene (109) and, consequently, of the HPG axis. Furthermore, in subcortical structures, CRH binds especially with the CHR-R2 receptor also present in testicular cells (110), which would explain why, in stress, there are apoptosis and age-related degeneration of Leydig cells (111) and inhibition of the conversion of androstenedione to TH (112). Moreover, *Romeo et al.* have shown that some key enzymes involved in the synthesis of catecholamines are present in Leydig cells, which could contribute to the regulation of spermatogenesis in times of stress (113). An experimental study validated the latter concept, showing that its effect on fertility depends on the type of stress and that it is not influenced only by adrenal hormones since the administration of TH did not affect the outcomes (114). In recent years, animal studies have confirmed the reduction of HPG axis functionality during stress, with a consequent decrease in GnRH, FSH and LH, and the testicular cells apoptosis occurs (115, 116).
One of the most noteworthy discoveries in this area was the β-Endorphin (β-EP) effect. It is produced by both hypothalamus and pituitary in the testis (117) and, in a stressful time, it inhibits the secretion of GnRH, with a reduction of LH (118), which in turn stimulates the synthesis of β-EP in the testis, suppressing TH and sperm production and inducing Leydig cells apoptosis (119).
In the included studies, sperm concentration was the most altered parameter, while sperm count, total motility and morphology were affected with reduced frequency. Even the temporal proximity between the stressful event and the semen quality impairment was reported. Indeed, an inverse relationship was reported between male infertility and perceived stress or several recent stressful life events (53, 56). Furthermore, *Boivin et al.* reported a higher number of treatment cycles for conception in women who reported more marital distress (54). In summary, the reported studies are promising, and others with higher evidence levels are desirable to ascertain the effect of psychological stress on male fertility.

Conclusions

Fertility is vulnerable to several environmental and occupational agents in men. Unlike chemical agents, which are more sectorial, physical ones are present in both well-resourced and developing countries.
Sedentary work has shown a remarkable capacity to cause male impairment in studies.
In addition to germ cells, even the testicular supporting ones are influenced by environmental exposure, such as Leydig ones, with alteration of the hormonal profile, including TH e and gonadotropins.
Despite these intriguing findings, a cause-effect relationship is hard to state due to the several confounders such as infections, smoking, previous surgeries and outdoor

pollution, and gaps in our knowledge to interpret studies for many agents. Considering the progressive reduction of male fertility worldwide, evaluation of the effect of physical agents on fertility is indispensable.

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