Environment International 138 (2020) 105627

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Gamete quality in a multistressor environment

Alessandra Gallo[a], Raffaele Boni[b], Elisabetta Tosti[a,*]

[a] Department of Biology and Evolution of Marine Organisms, Stazione Zoologica Anton Dohrn, Villa Comunale 1, 80121 Napoli, Italy
[b] Department of Sciences, University of Basilicata, 85100 Potenza, Italy

ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Gamete quality
Environmental stress
Fertilization
Xenobiotic
Climate change
Life style

ABSTRACT

Over the past few decades, accumulated evidence confirms that the global environment conditions are changing rapidly. Urban industrialization, agriculture and globalization have generated water, air and soil pollution, giving rise to an environment with a growing number of stress factors, which has a serious impact on the fitness, reproduction and survival of living organisms. The issue raises considerable concern on biodiversity conservation, which is now at risk: it is estimated that a number of species will be extinct in the near future. Sexual reproduction is the process that allows the formation of a new individual and is underpinned by gamete quality defined as the ability of spermatozoa and oocytes to interact during fertilization leading to the creation and development of a normal embryo.

This review aimed to provide the current state of knowledge regarding the impact of a broad spectrum of environmental stressors on diverse parameters used to estimate and evaluate gamete quality in humans and in canonical animal models used for experimental research.

Effects of metals, biocides, herbicides, nanoparticles, plastics, temperature rise, ocean acidification, air pollution and lifestyle on the physiological parameters that underlie gamete fertilization competence are described supporting the concept that environmental stressors represent a serious hazard to gamete quality with reproductive disorders and living organism failure. Although clear evidence is still limited, gamete capacity to maintain and/or recover physiological conditions is recently demonstrated providing further clues about the plasticity of organisms and their tolerance to the pressures of pollution that may facilitate the reproduction and the persistence of species within the scenario of global change.

Changes in the global environment must be urgently placed at the forefront of public attention, with a massive effort invested in further studies aimed towards implementing current knowledge and identifying new methodologies and markers to predict impairment of gamete quality.

1. Introduction

The environment is an integrated bio-geo-physical system, and it represents the final sink for numerous contaminants that are produced by the rapid growth of anthropogenic activities. Multiple interconnected environmental changes are now taking place, including chemo- physical pollution and climatic modifications that in turn contribute to deteriorating fresh/marine waters, forests, fisheries and soil, culminating in a general loss of biodiversity (Frumkin and Haines, 2019; Pimm et al., 2014). This an ongoing process: contaminated conditions appear to interfere with intricate reproductive mechanisms and events, creating problems in reproduction for a variety of species. Reproduction is a complex process of cell-to-cell interaction, initiated with the production of gametes (spermatogenesis and oogenesis) and leading to formation of the zygote, the first cell of a new individual. Gametogenesis is the process that transforms immature germ cells present in the gonads into mature gametes; it is underpinned by meiosis, the specialized process of cell division that allows chromosome number to be halved, with formation of haploid sperm cells and oocytes. By the end of gametogenesis, gametes are competent for fertilization but remain in a quiescent state until the process is reactivated by a reciprocal interaction with the other partner. Gamete activation is an essential pre-requisite for successful fertilization and subsequent embryo development, involving physiological events that are specific to either the sperm or the oocyte. Sperm activation is a multistep process induced by the extracellular coats of the oocyte, involving modifications in morphology and function. These modifications allow sperm to become motile, to be attracted towards the oocyte, bind to it, undergo the acrosome reaction (AR) and, finally, to fuse with the oocyte plasma membrane. This is followed by release of a sperm factor into the

* Corresponding author at: Department of Biology and Evolution of Marine Organisms, Stazione Zoologica Anton Dohrn, Villa Comunale, 80121 Naples, Italy.
E-mail address: tosti@szn.it (E. Tosti).

https://doi.org/10.1016/j.envint.2020.105627
Received 23 December 2019; Received in revised form 28 February 2020; Accepted 29 February 2020

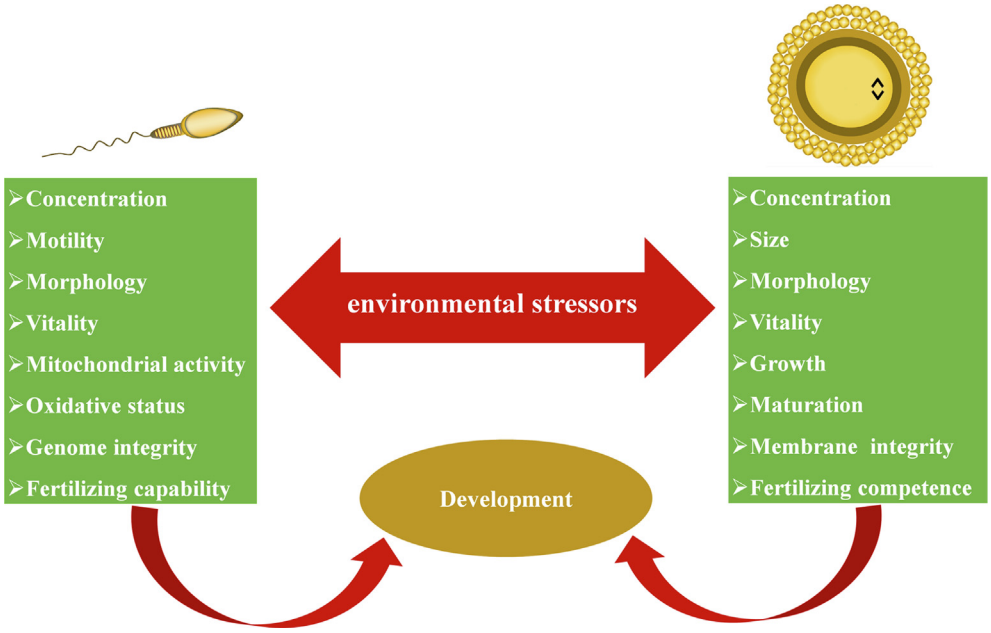


Fig. 1. Environmental stressors impact on gamete quality. Environmental stressors affecting different gamete quality parameters impair embryo development.

ooplasm, which immediately activates the oocyte in a process underpinned by electrical, structural and metabolic modifications (Dale et al., 2010; Tosti and Ménézo, 2016). All of these events involve regulatory molecules, ion fluxes and messenger mobilization. Although the specific events differ between species, comparative studies reveal that the majority share common mechanisms. However, since modalities of fertilization differ between species with external fertilization (marine animals), and internal fertilization (mammals), the variety of stressors prevalent in a particular environment will clearly have different impacts upon normal gamete physiology and behavior (Fig. 1).

Gamete quality is defined as the ability of spermatozoon and oocyte respectively to fertilize and be fertilized, leading to the development of a normal embryo (Bobe and Labbé, 2010). Successful fertilization is associated with the quality of the resulting zygote, which is in turn contingent upon the health of the oocyte and spermatozoon. Recent studies clearly confirm a close relationship between infertility and gamete health (Budhwar et al., 2017).

Despite the considerable effort invested in identifying possible predictive markers of gamete quality, the cellular and molecular factors involved remain largely unknown.

The health status of the spermatozoon is currently examined by investigating parameters that underlie fertilization capacity, using a conventional spermiogram with reference to the cut-off values provided by the WHO manual for semen assessment (WHO, 2010). These include sperm concentration, motility, viability and morphology. Sperm motility facilitates sperm travel toward the oocyte and the subsequent process of fertilization; poor sperm motility is considered to be a major cause of male infertility (McLaren, 2012). Abnormalities in some factors and regulatory pathways, together with specific gene defects, may impair sperm motility, with a subsequent impact on fertility. A recent review has identified some of these potential factors to include calcium and cAMP-dependent protein kinase and phosphatases pathways, reactive oxygen species (ROS) and the regulation of cell volume and osmolarity (Pereira et al., 2017).

The majority of recent studies evaluating sperm quality also included other parameters: (i) mitochondrial activity, which provides energy for sperm motility and (ii) tests of genome integrity such as chromatin condensation and DNA fragmentation. Chromatin condensation is a fundamental part of mammalian spermatogenesis that allows compaction of the sperm genome and that may lead to developmental arrests immediately post fertilization due to the fact that the oocytes are poorly able to fix tertiary structure anomalies. However, sperm chromatin remodeling is also epigenetically modified and especially the methylation errors have a major impact for the fertility of the next generations (Lees-Murdock and Walsh, 2008) passing this information from gamete to offspring (Gold et al., 2018).

DNA fragmentation plays an important role in the etiology of male infertility, and is mainly due to reactive oxygen species (ROS) that are produced as a result of cellular metabolism. At low levels ROS are involved in physiological sperm function as the acrosome reaction, but an imbalance between redox status and antioxidant defense generates oxidative stress, which impairs essential reproductive processes, whereas controversial studies report an impact on fertilization and pregnancy outcome (Bisht and Dada, 2017; Evenson and Wixon, 2008). The evaluation of oocyte quality is of course more difficult, so far evaluated mainly by direct counts in brooding species and by morpho-histological parameters.

This is a further matter for concern in human reproduction, since females appear to be more vulnerable to toxicity, with significant effects on fecundity and potential disruption of reproductive processes as well as subsequent fetal development (Brohi et al., 2017). However, it must also be considered that the oocyte has a rather good DNA repair capacity towards oxidative stress insults (Menezo et al., 2007).

Many of the parameters identified as targets of environmental insults may be useful biological markers of gamete competence, indicative of gamete reproductive potential (Ruvolo et al., 2013). In this respect, a large number of epidemiological studies have tried to identify possible sources of environmental stress that impair gamete quality, and the physiological parameters that may be targets of adverse effects related to stressors. Most of these parameters have been identified as end-points associated with idiopathic infertility and low *in vitro* fertilization success.

We describe below some of the main environmental stressors that are known to influence either sperm or oocyte quality, the morpho-functional aspects that are impaired and the resultant impact on fertilization and embryo development in most of the animal species studied, as well as in humans (Figs. 2–4).

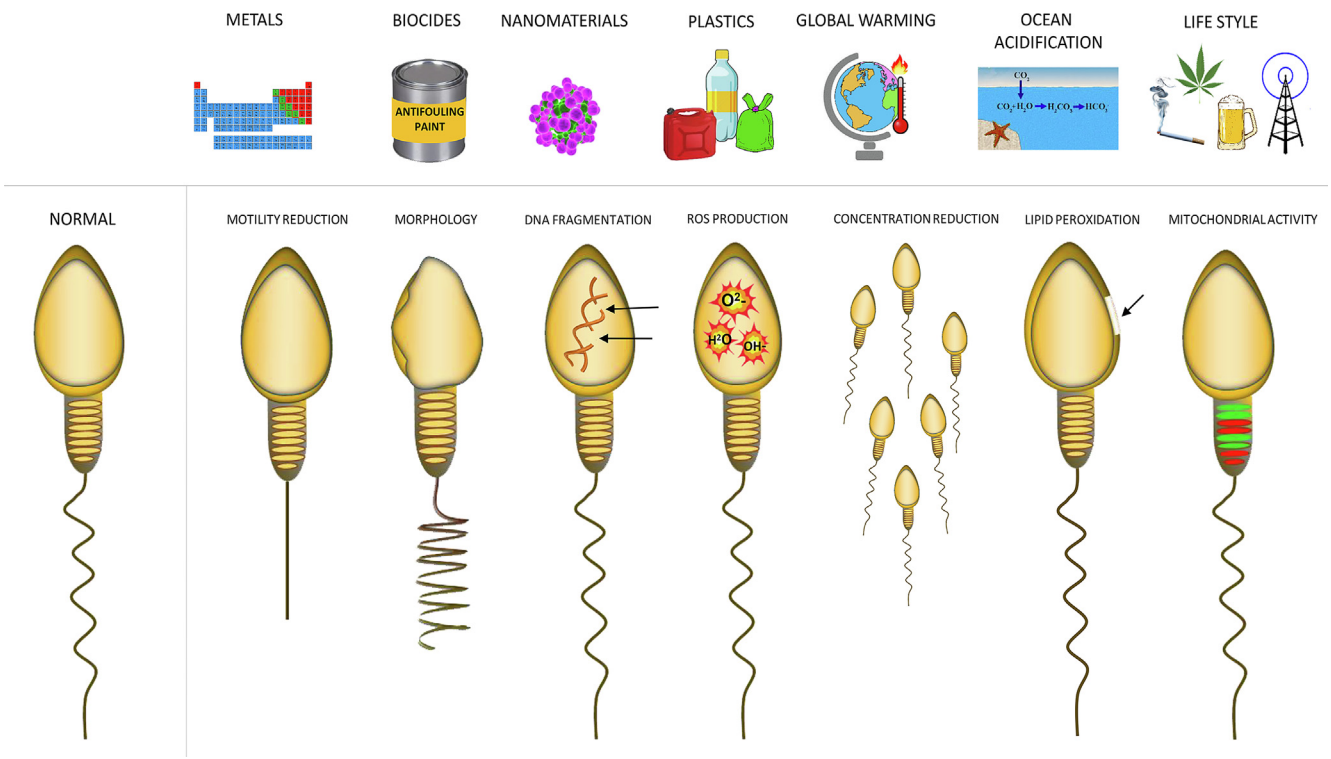


Fig. 2. Environmental stressors impact on sperm quality. Different environmental stressors alter sperm motility, morphology, concentration, mitochondrial activity and induce DNA fragmentation, plasma membrane lipid peroxidation and ROS formation.

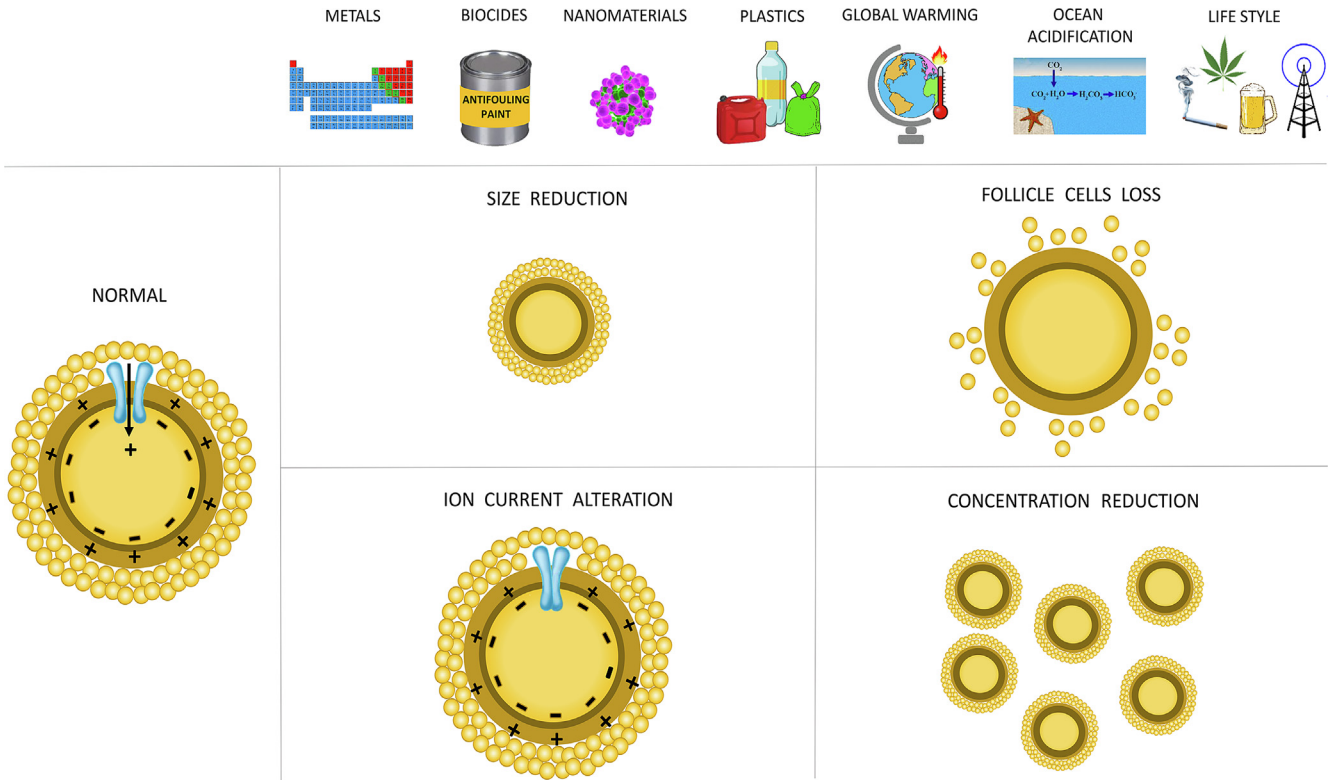


Fig. 3. Environmental stressors impact on oocyte quality. Different environmental stressors alter oocyte size, morphology, concentration and plasma membrane electrical properties.

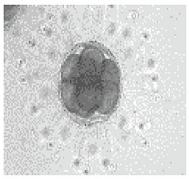
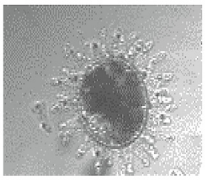
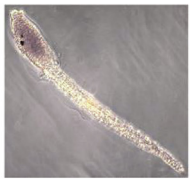
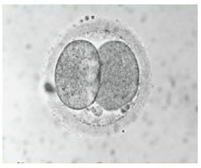
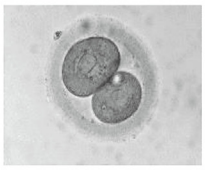
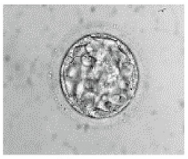
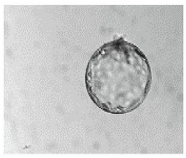
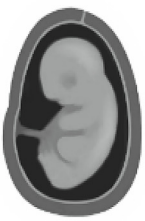
SPECIES	Normal development	Stress-induced abnormal development	References
Ascidians 	 8-cell embryo		Gallo et al., 2011 Gallo et al., 2013 Gallo and Tosti, 2015 Gallo et al., 2016
	 larva		Gallo et al., 2011 Gallo et al., 2013 Gallo and Tosti, 2013 Gallo and Tosti, 2015 Gallo et al., 2016
Sea urchin 	 larva		Manzo et al., 2013 Gambardella et al., 2013 Migliaccio et al., 2015 Oliviero et al., 2019
Mammals 	 2-cell embryo		Zenzes, 2000 Tablot and Liu, 2011 Ferreira et al., 2011 Zhao, 2017 Huang et al., 2018
	 blastocyst		
Human 	 fetus		Schagdarsurengin and Steger, 2016 Brohi et al., 2017

Fig. 4. Environmental stressors impact on embryo development. Environmental stressors impair embryo development in different marine invertebrates, mammals and human.

2. Impact of environmental stressors on gamete quality

2.1. Xenobiotics

Over the last few decades, agricultural production and manufacturing processes have released a number of diverse substances into the environment. These compounds are collectively known as xenobiotics, and include metals, herbicides, pesticides, persistent organic pollutants, antifoulants, nanoparticles, pharmaceuticals, and plastics (Wurl and Obbard, 2004).

Contaminants are transmitted to organisms via marine, ground and drinking waters, with a threat to their fitness, health, reproduction and even survival (Ritter, 2002). Most of the xenobiotics act as endocrine disruptors (EDCs), posing risks to animals and humans by targeting

different organs and systems in the body through mechanisms that interfere, mimic or block the natural actions of hormones or their receptors (Maqbool et al., 2016).

In vertebrate species, EDCs can interfere with both genomic and non-genomic pathways. Based on the capacity to mimic hormone actions, different EDCs affect fish reproductive physiology by inhibiting gametogenesis and decreasing rates of fertility. Sperm parameters such as density, motility, and fertility potential were shown to be altered in several wild species, and impairment of oocyte growth and maturation result in a generalized poor outcome after fertilization. These findings support the concept that interference with steroidogenesis and hormone synthesis pathways may affect gamete viability and quality, the major indicators of reproductive endocrine disruption (Carnevali et al., 2018). On this basis, gamete physiology appears to be a major target of several xenobiotics and EDCs that may induce a subsequent decline in both male and female fertility.

2.2. Metals

Metals are classified as essential or nonessential elements. Essential metals include magnesium, nickel, cobalt, copper, calcium, manganese, potassium, sodium and zinc; these participate in physiological processes, and are required by organisms in small quantities; however, they may have toxic effects when present in excessive quantities (Falchuk and Montorzi, 2001). Nonessential metals include aluminum, lead, cadmium and mercury; although these are tolerated by organisms at very low levels, they have no biological role and interfere with physiological processes to exert toxic effects on living organisms. In recent years, a large number of studies have investigated adverse effects of metals both on the environment and in human beings, but only a few have evaluated their impact on gamete quality.

Adult male mice given drinking water with lead (Pb) added to it for 6 months experienced serious impairment of sperm parameters, including density, viability, motility and morphology as well as compromised DNA structure and integrity. These effects, together with changes observed in testis and epididymis morphology suggest that Pb induces a significant decline in male fertility (Liu et al., 2018).

The effect of cadmium (Cd) has been investigated in mammals, and shown to cause a variety of types of damage to reproductive tissues and organs (Marettová et al., 2015). Specifically, injection of cadmium into adult mice and rats had short and long-term impacts on sperm motility, concentration, morphology, DNA integrity and also induced a premature acrosome reaction (Adamkovicova et al., 2016; Oliveira et al., 2009).

In mouse and human, effects were related to duration of exposure. The decrease in sperm motility observed after long-term exposure was not found after short exposure; both however resulted in a decreased fertilization rate (Zhao et al., 2017). A number of epidemiological studies found an association between cadmium, decreased sperm motility and fertility impairment. A recent study that aimed to elucidate the mechanism of toxicity suggested that a cadmium-induced tyrosine phosphorylation event was involved (Wang et al., 2016).

Metal pollution has been shown to cause male infertility through mechanisms that involve ROS production. Human spermatozoa exposed to the three different metals cadmium, lead and aluminum showed significantly decreased sperm motility; aluminum caused plasma membrane lipid peroxidation due to oxidative stress induced by ROS (Jamalan et al., 2016). Likewise, environmental exposure of human sperm to a battery of 5 metals showed an inverse correlation with progressive and total sperm motility, with the exception of zinc, which appeared to be beneficial for sperm concentration only (Wang et al., 2017b). These data support previous studies reporting that zinc has a physiological role in male reproductive health, due to protective activity during spermiogenesis, zinc finger proteins role in transcription and the stabilization of DNA structure. Moreover the toxicity of other metals is associated with their displacement of zinc resulting in destabilization of the tertiary structure of DNA (Barbato et al., 2017; Jeng et al., 2015; Kasperczyk et al., 2016).

Sperm morphology is also affected by different metals. Potassium chromate administered to mice induced an increase in teratospermy and decrease in sperm motility, but no damage to DNA or chromatin integrity was detected (Oliveira et al., 2010). Similarly, a copper-dependent increase in sperm head malformations was reported in mice, although this was not associated with a decrease in sperm viability (Zhang et al., 2016). Metals are one of the major sources of marine water pollution; this poses a particularly high risk, as both adults and spawned gametes are directly exposed to contamination. In the mussel *Mytilus galloprovincialis*, copper at subtoxic concentrations was recently shown to affect protamine-like proteins, the basic component of sperm chromatin; this subsequently had a negative effect on the reproductive system of this species (Lettieri et al., 2019b). Similarly, in the same species cadmium accumulation in protamine-like proteins was observed after parental exposure, suggesting that this metal induces a structural rearrangement of sperm nuclear components that will have a negative impact on chromatin organization (De Guglielmo et al., 2019). In other aquatic species such as the freshwater crab, different concentrations of lead reduced the integrity of the sperm plasma membrane, acrosomal membrane and DNA, all associated with a significant decrease in total antioxidant activity; the dose-dependent adverse effect of lead may be mediated by oxidative stress (Li et al., 2016a).

Nearly two decades ago, reduced sea urchin oocyte size and poor sperm quality were observed following chronic exposure to cadmium (Au et al., 2001). Migliaccio et al. investigated the effect of cadmium and manganese exposure on sea urchin females, revealing impaired fertilization with subsequent abnormal embryo morphology, related to nitric oxide production (Migliaccio et al., 2015). Ascidian oocytes were exposed to a set of six metals (lead, cadmium, mercury, zinc, tin, nickel), and the impact of each metal was evaluated by examining the electrical events that underlie the oocyte activation, fertilization, embryo and larval development. Different types of impact were observed, from an overall reduction in sodium current activity to reduction of the cleavage rate, reduction or inhibition of fertilization and absence of larval formation. However, only cadmium showed no effect on fertilization or normal embryo and larval development (Gallo, 2018; Gallo et al., 2011).

Different studies have demonstrated that oocytes are apparently more tolerant to metal insults. In non-mammalian species such as seabirds, cadmium and mercury were shown to accumulate in oocytes at different rates, depending on breeding seasons, oceanographic conditions and continental runoff. However, the oocytes showed concentrations of these metals at levels above the threshold for exerting a negative impact on reproduction and subsequent species persistence (Ceyca et al., 2016). Furthermore, oocytes have been reported to have a high tolerance to cadmium in a range of marine species (Pavlaki et al., 2016).

A set of metals were recently reported to induce a change in the size and volume of magpie (*Pica pica*) oocytes (Zarrintab and Mirzaei, 2017). Exposing livestock cumulus-oocyte complexes to cadmium even at nanomolar concentrations induced oxidative damage resulting in impaired oocyte fertilization (Martino et al., 2017). In humans, a recent pilot study correlated high copper, zinc, chromium and low iron levels, with reduced sperm motility and antioxidant defenses and the occurrence of increased sperm DNA fragmentation. Since these negative impacts were associated to men living in highly polluted areas it was suggested to use human semen as early sensitive biomarkers of environmental pollution in biomonitoring studies (Bergamo et al., 2018; Bergamo et al., 2016).

Altogether, these data support the concept that the effect of metals is greater on sperm than on oocyte quality; cadmium has been shown to exert a toxic effect on sperm motility in all species studied so far.

2.3. Biocides

Biocides are substances that have an influence on a wide range of biological processes, from growth retardation to death of the organism. Biocides include pesticides, bactericides, fungicides, herbicides, insecticides and antifouling compounds. A two-year comparative study that investigated sperm quality from men living in areas with heavy agricultural pesticide contamination *vs* men living in industrial towns revealed a close association between pesticides in current use and reduced semen quality (Swan, 2006). An epidemiological study later highlighted the fact that pesticides, including 1,2-Dibromo-3-Chloropropane i.e. DT/Dichlorodiphenyldichloroethylene, ethylenedibromide, organophosphates, and polychlorinated biphenyls (PCB) consistently exerted an effect on sperm physiology. PCB in particular was detrimental to sperm count and motility, suggesting a link between ambient air pollutants and semen characteristics. There is further evidence that endosulfan, an organochlorine pesticide, is toxic to reproductive processes of aquatic life, especially in freshwater organisms (Han et al., 2011). An endosulfan-induced alteration in spermatocyte/spermatid clumping patterns was demonstrated, accounting for a subsequent low sperm concentration after spermatid differentiation to mature spermatozoa (Islam et al., 2017).

Antifoulants play a key role amongst the biocides; these are chemical substances added to paints in order to counteract organisms that cause marine biofouling on submerged components of boats, ships and aquaculture infrastructures. These substances release harmful particles that may affect non-target organisms, and this represents a major source of concern. Historically, the organic booster tributyltin (TBT) was the most commonly used biocide in antifouling paints. TBT was soon recognized as harmful to marine environments by disrupting endocrine systems of both aquatic life and wildlife. In particular, TBT affected mollusk reproduction by generating imposex, the irreversible induction of male sex characteristics in females (Amara et al., 2018; Smith, 1981). Due to its high reprotoxicity, the use of TBT use was globally banned by 2008, and this led to a search antifoulants that are less harmful for the environment and biota, with the formulation of alternative biocides such as diuron and chlorothalonil. In the late 1990 s, TBT was shown to impede early sperm-egg interactions in ascidians through a mechanism involving a reduction in oocyte plasma membrane ion currents, which support the key role of ion channel activity in gamete physiology (Franchet et al., 1998). It was also later tested the effects of TBT and diuron on gamete quality in the ascidian *Ciona intestinalis* (Gallo and Tosti, 2013). Consistent with the toxic effect of TBT, it was demonstrated an impact on electrical properties of the oocyte plasma membrane that underlie oocyte activation, followed by a short-term effect on events during fertilization and a long-term effect on larval development. In contrast, diuron also affected electrical properties by reducing the amplitude of plasma membrane sodium currents; however, this was not followed by further impairment of fertilization rate and transmissible damage to offspring. It was also tested the effect of a new antifoulant, chlorothalonil, on *C. intestinalis* oocyte quality, showing that mature oocytes underwent a decrease in the amplitudes of the sodium and fertilization currents followed by arrest of embryo development at high chlorothalonil concentrations (Gallo and Tosti, 2015). Exposure of oyster gametes to diuron revealed a significant genotoxic effect, but this was not accompanied by impairment of sperm mitochondrial activity and acrosomal membrane integrity (Akcha et al., 2012). Closely related to the direct impact of antifoulants, paint has recently been claimed to have harmful effects due to the presence and release of nanosized copper and zinc particles (Adeleye et al., 2016).

2.4. Herbicides

Herbicides are used in agriculture, and long-term exposure of organisms to these compounds raises particular concern. Atrazine, classified as a potential endocrine disruptor, is widely used. In crayfish, atrazine causes dysregulation of hormone synthesis in the ovary, resulting in reduced oocyte size (Silveyra et al., 2018). A survey following three generations of rats exposed to atrazine demonstrated epigenetic alterations in oocytes and sperm, followed by a capacity to promote a range of developmental diseases with transgenerational epigenetic inheritance (McBirney et al., 2017).

Glyphosate is another emerging toxic herbicide, and this has been tested on gametes and embryos of the common carp *Cyprinus carpio L*. A commercial glyphosate preparation reduced oocyte swelling and exerted a minor toxic effect on sperm motility at low concentrations, but motility was impaired at higher concentrations. Long-term effects included reduced embryonic survival without affecting rate of development; however clear embryo malformations and poor larval quality were reported (Lugowska, 2018). Results regarding glyphosate reprotoxicity are still controversial; however, a recent systematic review and *meta*-analysis disclosed an association between glyphosate exposure and reproductive impairment in rodents, with a significant decrease in sperm concentrations (Cai et al., 2017).

Propoxur, a carbamate pesticide, has recently been shown to exert a further reprotoxic effect on sperm density in rats (Kenfack et al., 2018). The results of this study confirmed a significant decrease in sperm density and in the total quantity of intratesticular proteins. However, no significant effects on reproductive performance and fertility were reported.

2.5. Nanoparticles

The rapid growth of nanotechnologies and nano-industry devoted to production and commercialization of electronics, catalytics, cosmetics and medical devices is causing widespread release of nanoparticles (NPs) into the environment (Weissig et al., 2014). NPs are nanomaterials characterized by their small size and specific physical-chemical properties that allow them to adhere to cell plasma membranes or to enter cells via transport systems. NPs in the environment can thus affect physiological processes in a variety of living organisms (Maurer-Jones et al., 2013). Recent studies report a wide range of effects in marine systems, due to the fact that seawater often represents the ultimate sink for NPs (Baker et al., 2014). There is evidence that NPs of silver, copper oxide, and zinc oxide severely affect a wide range of organisms, from algae to mammalian cell lines (Bondarenko et al., 2013). To date, little is known about the impact of NPs on gamete quality. In mussels, spermatozoa exposed to zero-valent nanoiron showed a 20% decline in successful fertilization, and 30% mortality; exposure to higher concentrations caused significant DNA damage (Kadar et al., 2011). Testing the nanoiron NPs on spermatozoa of different marine species identified a species-specific impact: exposure of ascidian spermatozoa led to serious disruption of embryo development. This impact was less evident in mussels, whereas no significant effect was detected in sea urchins compared to controls (Kadar et al., 2013).

The impact of silver, titanium oxide and cobalt NPs on sea urchin sperm was also investigated by analyzing functionality, morphology and biochemistry of early developmental stages following exposure. Although no effect on fertilization events was observed, developmental anomalies in embryos from the gastrula to pluteus larval stages, together with skeletogenic alterations were observed (Gambardella et al., 2013). Interestingly, in buffalo, a species that is evolutionary distant from marine invertebrates, titanium oxide NPs exerted similar cytotoxic effects on sperm function, causing a high level of DNA fragmentation (Pawar and Kaul, 2014).

Zinc oxide, another widespread NP, affected sea urchin sperm fertilization slightly, with resulting skeletal alterations in the offspring and early block of subsequent larval development that were strictly related to sperm DNA damage (Manzo et al., 2013; Oliviero et al., 2019).

Although zinc oxide NPs were reported to exert a dose-dependent cytotoxic impact on human sperm (Barkhordari et al., 2013), other

studies contradicted this negative impact, demonstrating a low, or no specific effect on spermatozoa. Zinc oxide NPs do not penetrate the sperm membrane, and their addition to cryopreservation medium appears to attenuate human sperm damage after thawing (Isaac et al., 2017).

Nickel nanoparticles are increasingly used in modern industries as catalysts, sensors, and in electronic applications. it was recently demonstrated that nickel and copper oxide NPs have the potential to induce spermiotoxicity in *C. intestinalis* and sea urchin, representing a threat to reproductive success in these species, with possible decrease in existing populations. In particular, nickel NPs generated mitochondrial dysfunction, altered sperm morphology and in turn oxidative stress, lipid peroxidation and DNA fragmentation in *C. intestinalis* spermatozoa (Gallo et al., 2016). Similar results were obtained after exposing *Paracentrotus lividus* spermatozoa to copper oxide NPs, with decrease in viability, impaired mitochondrial activity, increased ROS production, lipid peroxidation, DNA damage and morphological alterations (Gallo et al., 2018).

The safety of some NPs is still debated, with conflicting data reported. An initial study reported that gold NPs are toxic to sperm, with nanoparticle penetration into the sperm head identified (Wiwanitkit et al., 2009). Moretti et al. provided evidence that neither gold or silver NPs appeared to be harmful for human spermatozoa (Moretti et al., 2013). This finding has recently been supported in mammals, since silver and gold NPs showed no impact on rat sperm chromatin integrity (Fathi et al., 2018) or on other sperm parameters such as motility, membrane integrity and morphology (Tiedemann et al., 2014). In contrast, both of these NPs were shown to induce detrimental effects in mice; in particular, gold NPs reduced sperm motility and normal morphology with a short-term impact on chromatin remodeling and stability (Nazari et al., 2016). Similarly, human and mouse spermatozoa treated with silver NP exhibited highly detrimental changes, including chromatin damage, marked ROS-induced DNA fragmentation, reduced membrane integrity and impaired mitochondrial activity (Lafuente et al., 2016; Mathias et al., 2015; Wang et al., 2017a).

Silver NPs were shown to be internalized into mouse sperm cells, with a serious cytotoxic effect leading to a long-term effect on fertilization and embryonic development (Yoisungnern et al., 2015). In the bovine, gold NPs decreased sperm motility through a different mechanism of action, involving an interaction between NPs and the surface of the sperm membrane (Taylor et al., 2014).

Conflicting results have also been provided for cerium oxide NPs, with some authors reporting beneficial effects. In diabetic mice, cerium oxide NPs were shown to ameliorate sperm DNA fragmentation (Artimani et al., 2018), and in the ram, no cold shock-induced damage to sperm motility or the integrity of membranes and DNA was observed (Falchi et al., 2018). However, these data were not corroborated by studies on human and mouse sperm, where cerium oxide NPs were shown to induce sperm abnormalities, DNA damage and a reduction in motility and concentration (Adebayo et al., 2018; Préaubert et al., 2018).

Although a large number of studies have been carried out to investigate the impact of NP on sperm physiology, this is not the case for oocytes, due to the difficulty of obtaining material for experimental investigation, especially in mammals and human. Although the potential toxic effects of NPs on female reproductive fitness is receiving increasing attention, few data are available to date. Recent findings from *in vitro* experiments revealed that silver NPs impair mouse oocyte maturation, affecting either fertilization rates or subsequent embryo development (Huang et al., 2018). In contrast to adverse effects seen in male gametes, several NPs appear to be beneficial for oocyte physiology. For example, adding different NPs to cryoprotectant medium may improve the efficiency of porcine oocyte vitrification, by acting on the properties of solutions (Li et al., 2016b). Similar positive effects have been noted for cerium oxide and silver NPs, which apparently improve the developmental competence of *in vitro*-matured ovine oocytes (Ariu et al., 2017), protect oocytes against oxidative stress (Courbiere et al., 2013) and promote zebrafish oocyte maturation (Chen et al., 2017). In contrast, cerium oxide NPs have been reported to induce a genotoxic effect in the mouse, with impairment of *in vitro* fertilization related to disruption of gamete interaction and generation of oxidative stress (Preaubert et al., 2015).

2.6. Plastics

For several decades, the presence of plastics in aquatic environments has been a cause for particular concern: islands of plastic litter have even been formed, and these migrate through oceans where they will affect the reproductive fitness of marine biota (Santos et al., 2015). Pollution by micro- and macro-plastics is one of the most alarming threats to the health of the environment and to human fitness, presently raising serious economic and health concerns all over the world. Plastics are synthetic organic polymers that have been used as basic constituents of a series of commercial products due to their versatility, strength and low cost: bags, bottles, food storage containers, personal care products and some types of drug delivery. When released into the environment, plastics are degraded to fragments < 5 mm in size (microplastics) and to nano-sized plastic debris (< 1 μm) (Gregory, 1996). Plastic industrial waste that ends up in water, air and soil remains there permanently due to continuous recycling (Kukulka et al., 2012). Many authors have shown that microplastics affect reproductive activity (Auta et al., 2017; Gardon et al., 2018); however, to date, very few have investigated the effect of plastics on gamete quality. During the last decade, phthalates in plastic goods have been shown to have an impact on sperm quality, with an association between phthalate levels and reduced sperm parameters such as concentration, morphology and motility (Duty et al., 2003; Hauser, 2006; Jurewicz et al., 2009; Wirth et al., 2008). In particular, clear adverse effects of two different phthalates were detected in human sperm motility, activation, penetration, and on the tyrosine phosphorylation signaling pathway, an essential regulator of sperm function (Gualtieri et al., 2005; Xie et al., 2019). Exposure of the adult oyster *Crassostrea gigas* to polystyrene microplastics affects fecundity by reducing oocyte number to 38% and sperm velocity to 23%, ultimately resulting in a negative impact on offspring growth (Sussarellu et al., 2016). In the same oyster, polystyrene nanoplastics are highly toxic to both gametes, seriously impairing embryo-larval development with numerous malformations and total developmental arrest (Tallec et al., 2018). These nanoplastics adhere to the surface of both gametes, and this may be the possible mechanism of their toxicity (González-Fernández et al., 2018). Bisphenol A (BPA) is a ubiquitous compound present in food and plastic storage containers, as well as containers used for infant feeding. Although there is conflicting evidence (Mínguez-Alarcón et al., 2016), it is now widely recognized that BPA acts as an endocrine disruptor. This feature is of increasing concern because of the association with reproductive disorders, ultimately threatening human fitness and health (Chianese et al., 2017; Tomza-Marciniak et al., 2018). Despite the high level of attention given to the toxic impact of BPA, only a few studies have evaluated its effect on human gamete quality. Environmental exposure to BPA has been shown to affect sperm and oocyte quality through epigenetic mechanisms that represent a risk for the resultant offspring and their reproductive ability. Even low dose BPA exposure has been shown to cause serious impairment of spermatogenesis, sperm parameters and DNA damage (Omran et al., 2018), as well as oocyte quality, growth, maturation, during both *in vivo* and *in vitro* fertilization (Machtinger et al., 2013; Wang et al., 2018).

2.7. Climate change

The functions of natural ecosystems and human economies are fundamentally dependent on climate. At present, climate change is defined as seasonal changes associated with increasing accumulation of

greenhouse gases in the atmosphere, in particular carbon dioxide (CO_2), with two different alarming consequences: global temperature increase (global warming) and ocean acidification (OA). Rising global temperature threatens species fertility, and in turn biodiversity and persistence, at some levels exerting an ecological and evolutionary impact known as 'thermal fertility limit' (Walsh et al., 2019). In recent years, several studies have addressed possible relationships between rising temperature and the reproductive output of animal species (Boni, 2019). Local Italian coastal seawater temperature changes have been associated with a decrease in reproductive potential of zooxanthellate coral, due to oocyte loss during gametogenesis. In particular, oocytes did not reach maturity at the warmest temperatures, possibly due to inhibition of metabolic processes (Airi et al., 2014).

In mytilids, both gametes were shown to be vulnerable to thermal stress, with impaired oocyte development detected after parental exposure to a gradual temperature elevation up to 28 °C (Múgica et al., 2015). Similarly, adult mussels subjected to the same temperature threshold had impaired sperm function, with a reduction in concentration, motility and mitochondrial activity, and increased lipid peroxidation and DNA fragmentation (Boni et al., 2016).

In insects, repeated experimental heatwaves reduced male fertility and sperm competition, exerting several different effects, including reduced sperm production, viability and migration in the female tract. A transgenerational impact and even male sterilization have also been found a further troubling cause for concern (Sales et al., 2018).

Based on these findings, it may be predicted that growing global temperature may shift reproductive cycles in mussels, significantly affecting their production for commercial use. Microcosm experiments that evaluated the effect of high temperature on ram spermatozoa demonstrated a significant alteration in sperm motility in terms of linearity and the average path velocity (De et al., 2017). In the past, *in vitro* maturation and fertilization of bovine oocytes were thought to be temperature-dependent processes (Lenz et al., 1983). Several studies later identified oocyte sensitivity to be due to thermal stress, affecting mainly processes during maturation (Hunter et al., 2017; Lopes et al., 2012). Even warm season temperature can affect oocyte developmental capacity to blastocyst (Al-Katanani et al., 2002), also inducing blastocyst fragmentation, decrease in mitochondrial DNA and increased expression of apoptotic genes (Ferreira et al., 2011; Ferreira et al., 2016).

Alterations in the kinetics of oocyte nuclear and cytoplasmic maturation were also reported, and insemination of these oocytes resulted in reduced blastocyst development (Edwards et al., 2005). A temperature above physiological homeostasis, such as 41 °C, affects bovine *in vitro* oocyte nuclear maturation by inducing apoptosis and impairing subsequent oocyte fertilization capacity. Cytoskeletal elements such as microtubules and microfilaments, involved in meiotic maturation and in the meiotic spindle, are disrupted by heat shock, and this may be responsible for altering the process of oocyte maturation (Ju et al., 2005; Roth and Hansen, 2005). A recent study in porcine oocytes examined whether short-term thermal stress might affect oocyte function and developmental competence. This thermal stress induced mitochondrial degradation and biogenesis but enhanced the oocyte mitochondrial membrane potential and ATP content, and improved their ability to develop to blastocysts (Itami et al., 2018).

Climate models have shown that the change in sea water salinity is a further side effect of global warming. Recent studies have confirmed that ocean surface salinity is affected by global intensification of the water cycle: abnormal increase in salinity is closely related to more evaporation, whereas more precipitation and ice melting induce a decrease in salt (Durack et al., 2012; Liu et al., 2018). The impact of salinity variation on marine gametes has demonstrated a generalized adaptation potential for sperm or oocytes, with reduced fertilization detected. Osmolality plays a fundamental role in sperm activation by inducing sperm motility after release into sea water. Spermatozoa of teleost fishes reared in fresh water, sea water and hypersaline water showed acclimatization to all the three conditions, with adaptive responses completed within two months (Legendre et al., 2016). Shorter longevity and lower sperm swimming speed that affected fertilization capacity was also observed in the euryhaline teleost *P. flesus*, suggesting that marine teleosts increase the number of spawned spermatozoa as an adaptation mechanism aimed towards sustaining fertilization capacity (Nissling and Larsson, 2018).

Recent studies demonstrated that mussel sperm submitted to different hypo-saline conditions had alterations in protamine-like proteins/DNA binding, highlighting the phenomenon of gamete plasticity as a strategy for fertility preservation (Lettieri et al., 2019a).

In contrast, oocytes appear to be more sensitive to alterations in salinity. Plerocercoid *S. solidus* oocytes developed normally in salinities of up to 12.5‰, but viability dropped rapidly above this, and no hatching was obtained at > 20‰ salinity (Simmonds and Barber, 2016). Reduced fertilization potential of both gametes in hypo-saline conditions confirmed previous findings reported in corals (Hédouin et al., 2015). However, apart from conditions of extreme hyper-salinity, oocytes were able to regulate their volume with respect to the osmolality of surrounding water (Hansen et al., 2012). In the sand dollar, both gametes were submitted to low salinity conditions in order to determine which gamete was responsible for diminished fertilization; reproductive failure was attributed to failure of fertilized oocytes to cleave, rather than inability of sperm to fertilize. This confirms that oocytes are more vulnerable, compared with the resilience exhibited by spermatozoa (Allen and Pechenik, 2010).

OA is the other facet of climate change that is a result of continuous uptake of atmospheric CO_2 into the seas, lowering global pH values of the ocean surface. Marine animals spawn their gametes into sea water, and they are thus subjected to a lowered pH (Foo and Byrne, 2017); however, the impact of acidified water on reproductive processes varies between species, sometime resulting in an enhanced fertilization that is suggestive of a novel process of natural selection (Schlegel et al., 2012).

The sensitivity of *C. robusta* spermatozoa after short-term acidified seawater exposure has been investigated providing a new evidence of resilience of ascidian spermatozoa in response to OA that opens a new scenario on the ascidian capacity to continue to reproduce and persist in changing oceans (Gallo et al., 2019). On the contrary, the exposure of *Mytilus galloprovoncialis* spermatozoa to OA prevent sperm motility activation, which may cause a fertilization success decrease with important implications for the fitness and the survival of marine invertebrates (Esposito et al., 2020).

Sea urchin spermatozoa have frequently been examined in order to test the impact of acidification on gamete quality, with conflicting results. In some sea urchin species, low pH significantly decreased the proportion of motile sperm (Schlegel et al., 2012), sperm swimming speed (Havenhand et al., 2008) and had a significant effect on fertilization and cleavage (Moulin et al., 2011). The reduced fertilization rate appears to be influenced by an initial alteration in sperm motility, velocity and path linearity, which in turn lowers the probability of sperm-egg collision and fusion (Campbell et al., 2017; Shi et al., 2017). Sperm competition is extremely important in sea water, although whether it is related to beneficial sperm performance is not yet fully understood. Although inter-individual variation in sperm populations has often been reported (Schlegel et al., 2014), in the sea urchin *P. lividus* rapidly motile spermatozoa successfully fertilize in natural conditions, and this does not occur under acidified conditions (Campbell et al., 2016). Sea urchin oocytes are surrounded by a jelly coat whose components promote sperm attraction toward the oocyte, optimizing the success of interaction and stimulating the acrosome reaction (Tosti, 1994). In order to clarify the effect of acidification on sperm-egg interaction, a recent study evaluated the effects of OA on oocyte extracellular structures. The oocyte jelly coat was reduced in acidified conditions, suggesting not only an adverse effect on sperm chemotaxis, but also interference with the oocyte block to polyspermy. This highlights the importance of oocyte chemistry in successful fertilization (Foo et al.,

2018), an impact of OA on marine gamete function that had not been previously appreciated. However, the jelly coat of different sea urchin species showed different sensitivities to OA, possibly associated with oocyte evolutionary mechanisms.

An increase in greenhouse gas emission induces changes in both temperature and OA; special attention is currently focused on detecting the impact of these interactive effects. Although studies reporting the combined effect of global warming and OA on gamete quality are not yet available, previous investigations in the sea urchin predict that low pH affects sperm density with reduced fertilization, but this was compensated for by an increase in temperature, which enhanced fertilization (Byrne et al., 2010; Ho et al., 2013). This observation suggests the possibility of reciprocal buffering effects, but also hints at the tolerance and resilience of gametes subjected to multiple environmental stress factors (personal communication).

2.8. Air pollution

Air quality is of the utmost importance for both general health and for the reproductive function of living organisms. Global air has been contaminated by a series of compounds released by industrial activity, diesel fuels and cigarette smoke. Most of the compounds, such as nitrogen and sulfur derivatives, heavy metals, polycyclic aromatic hydrocarbons and particulate matter act as endocrine disruptors that can alter the male reproductive system; spermatogenesis appears to be particularly prone to genetic and epigenetic alterations (Vecoli et al., 2016). Over the last few decades, a link between ambient air pollutants and sperm parameter impairment has been reported (Jurewicz et al., 2009; Rubes et al., 2005). Studies on animals and humans have provided strong evidence that airborne particulate matter is particularly genotoxic to male germ cells, resulting in DNA damage, abnormal sperm morphology and altered sperm performance (Somers, 2011); in addition, the development and function of testicular tissues can be affected by impaired intercellular communication in testicular junctions (Kubincová et al., 2019). A troubling secondary effect was also identified: parents who are smokers can transmit altered sperm DNA to preimplantation embryos, with an increased risk of childhood cancer (Lafuente et al., 2016b; Zenzes, 2000). However, a survey that also took into account the effects of different outdoor air pollutants on sperm function parameters reported conflicting data, suggesting a lack of consistency so that results are not comparable (Lafuente et al., 2016b). Nonetheless, two recent systematic reviews (Carré et al., 2017; Menezo et al., 2019) confirmed that air pollution has a direct effect on sperm motility, morphology, vitality, DNA integrity and other parameters required for a normal outcome of reproduction. Most of the studies quoted utilized spermatozoa as the gamete model, since they are easily collected. However, a few studies have also demonstrated an adverse impact on the oocyte meiotic spindle and ovarian follicular reserve after exposure to cigarette smoke and polycyclic aromatic hydrocarbon from cigarette combustion, resulting ultimately in possible chromosome errors and premature onset of menopause (Zenzes, 2000).

2.9. Lifestyle

Tobacco smoke, drugs and alcohol consumption in combination with occupational hazards represent unfortunate habits that are modifying lifestyle all over the world, with general deterioration of reproductive function as a result (Sansone et al., 2018; Sharma et al., 2013). Male and female gametes possess their own specific epigenomes, and several studies have shown that the germline is affected by epigenetic events. Parental lifestyle can alter maternal and paternal genomes, giving rise to heritable epigenetic changes that in turn may impair the health of offspring (Gold et al., 2018; Schagdarsurengin and Steger, 2016). Tobacco smoking not only contributes to air pollution, but is also a part of negative lifestyle and social behaviors that affect gamete physiology and function, irrespective of gender status. The heavy burden of toxicants contained in cigarette smoke can target almost all stages of reproductive activity. Both animal models and patients attending for *in vitro* fertilization treatment demonstrate negative effects of cigarette smoke on gamete quality, as well as on crucial steps of fertilization such as the acrosome reaction and sperm binding to the zona pellucida (Dechanet et al., 2011; Talbot and Lin, 2011). Nearly a decade ago, cigarette smoke extracts were tested on human sperm parameters, revealing concentration- and time-dependent motility suppression and reduction of mitochondrial membrane potential. Effects on genomic integrity and induction of apoptosis together with the formation of DNA adducts were also suggested (Calogero et al., 2009). A survey of 10,823 infertile smoking and non-smoking males demonstrated an association between cigarette smoke and lower sperm count, with a higher incidence of morphological defects in smokers; however, other parameters such as pH, motility and hormone production were not affected (Bundhun et al., 2019). These authors confirmed previous *meta*-analyses suggesting a generalized deterioration of semen quality in either moderate or heavy smokers, and an overall negative effect on conventional semen parameters other than sperm chromatin condensation and viability. These abnormalities were also shown to be strictly related to dose, time and duration of exposure (Mostafa et al., 2018; Sharma et al., 2016). The adverse effect of tobacco is of greater concern in females, because of the limitation imposed by the fact that a finite reserve of oocytes is established in the ovaries at birth. The damage produced by components of cigarette smoke on a limited number of gametes may seriously harm adult reproductive capacity. Tobacco has in fact been shown to exert adverse effects on folliculogenesis and oocyte quality both in animals and in women (Budani and Tiboni, 2017; Mai et al., 2014). Accelerated follicle loss, abnormal follicular growth and impaired oocyte morphology and maturation has been reported in female smokers, and this in turn appeared to affect the long-term fertility of female progeny. Transmission of smoking-induced sperm DNA alterations have been found in pre-implantation embryos, and this poses a risk of malformations, cancer and genetic diseases in progeny.

Habitual drug use poses a further risk to human health as well as reproductive fitness and outcome. Marijuana smoking is widespread in numerous countries; a 7-year longitudinal study examined semen quality in more than one thousand semen samples from men who had smoked marijuana. Although a generally deleterious effect of marijuana on testicular function had been previously reported, the findings of this study were not consistent with this observation; in fact, marijuana smokers exhibited higher sperm concentrations compared to a population that had not consumed marijuana. However, other sperm parameters were found to be under the threshold of WHO standards for semen assessment. Despite these reassuring results, the authors speculate that they may not be generally applicable to men in the global population (Nassan et al., 2019). Cannabinoids are active components in marijuana that are known to modulate reproductive events in mammals; they bind to receptors in the reproductive system, competing with hormonal regulation. Endocannabinoids have been shown to exert different noxious effects on male reproduction by inhibiting sperm motility and capacitation, and by inducing a precocious acrosome reaction, possibly also interfering with sperm mitochondrial activity (Francou et al., 2017). Although therapeutic opioid administration for pain management is accepted worldwide, heroin consumption may also be recreational, especially in young people. Direct human sperm exposure to opioid analgesics has a toxic effect on sperm motility *in vitro,* with repercussions for male reproductive health (Xu et al., 2013). Although ethical considerations make investigation of male cohorts difficult, studies in which patient consent was obtained revealed a significant negative correlation between opiate consumption in adult men and semen quality, sperm function, seminal plasma antioxidant capacity, and sperm DNA integrity (Drobnis and Nangia, 2017; Safarinejad et al., 2013). More recently, disclosure of clinical aspects in male active heroin users related to male reproductive parameters provided valuable new insights about correlations between opiate addiction, semen

parameters and hormone levels. This investigation revealed a significant association between heroin use and impaired spermatogenesis, semen parameters and in particular alteration of histone-to-protamine transition ratios that form the basis of sperm chromatin condensation. The parameter that was most greatly affected was semen pH, which in turn can decrease sperm viability and motility; opiate receptors are present in regions of the sperm cell involved in motility, and heroin addiction apparently causes an anti-motility effect (Nazmara et al., 2019). Cocaine is another widely used recreational drug whose constant use may affect both spermatogenesis and ovarian response (Sharma et al., 2013); however, to date the effect of cocaine on gamete quality has not been investigated in any detail. Alcohol abuse has been suggested to have an impact on fertility, causing poor semen production and apoptosis-related sperm chromatin disorders. In rats, chronic ethanol consumption impairs sperm motility, nuclear maturity and genome integrity (Talebi et al., 2011); however, recent investigations also demonstrated a relationship between alcohol consumption and a generalized reduction in semen quality including volume, sperm concentration, motility, morphology and increase in DNA fragmentation (Borges et al., 2018; Muthusami and Chinnaswamy, 2005). A systematic review and *meta*-analysis of the effects of alcohol intake on human reproductive fitness distinguished between moderate, occasional and high consumers, showing that only high daily alcohol consumption was related to adverse effects on semen volume and sperm morphology (Ricci et al., 2017). Although women who regularly consume alcohol may experience infertility, a clear effect of alcohol on oocyte physiology is at present not available in the literature.

Intense use of modern technologies has led to a rapid change in the lifestyle of young people. Electronic pollution is a growing concern, since the 21st -century human being is literally surrounded by high levels of radiofrequency electromagnetic fields (RF-EMF) and ionizing radiation that emanates from several types of devices such as mobile phones, cell phone towers, radar, laptops, wireless (Wi-Fi) and microwave ovens (Kesari et al., 2018). In order to assess the safety of these devices, numerous studies have evaluated their impact on fertility potential, starting with studies conducted in mammals. The vulnerability of human spermatozoa to RF-EMR was investigated in pilot studies initiated a decade ago, which highlighted that continuous exposure to radiation is harmful, inducing a decline in sperm motility, viability and a reduction in total antioxidant capacity associated with increased ROS levels, leading to DNA base adduct formation and ultimately DNA fragmentation (Agarwal et al., 2009; De Iuliis et al., 2009). These effects were later confirmed in mice, rats, rabbits and human sperm exposed to magnetic fields, resulting in a deterioration of sperm quality in terms of count, motility, morphology and the generation of DNA damage, as well as apoptosis induced via a possible increase in oxidative stress (Adams et al., 2014; Kesari et al., 2013; La Vignera et al., 2012; Wright et al., 2014). Very few studies have investigated human oocytes; however, studies on chicken eggs exposed to the immediate environment of a cell phone demonstrated an increase in embryo mortality rather than clear damage to the gamete itself. The ubiquitous use of cell phones means that it is difficult to establish reliable control groups for human studies, and therefore results are often inconsistent and conflicting (Merhi, 2012). Testing the direct impact of laptop computers connected to local Wi-Fi networks on human spermatozoa revealed a significant decrease in progressive sperm motility and increase in DNA fragmentation (Avendaño et al., 2012); keeping a computer connected wirelessly to the internet may adversely affect regions that are close to the testicles, also compounded by heat produced by the battery. With the introduction of new technologies, electromagnetic waves from 3G + WiFi modems have been adopted and widely used. An initial investigation of the effect of these specific waves demonstrated a further significant decline in human sperm motility and kinetics (Kamali et al., 2017). In addition to the factors related to lifestyle, some occupational agents also influence both spermatogenesis and male reproductive functions. Sperm quality is not only affected by environmental insults, but also by factors in the workplace. Men exposed to high levels of X-rays and heat are at risk of a reduced sperm count. This is particularly evident when testicles are exposed to high temperatures from industrial machinery, ovens and regular sauna use (Garolla et al., 2013; Hamerezaee et al., 2018). Furthermore, a sedentary work position may contribute to increased scrotal temperature, which appears to be negatively associated with sperm concentration (Hjollund et al., 2002). Although controversial, fertility parameters have been shown to be impaired in professional drivers and in young men who wear tight clothing around the thighs: further *in vitro* and *in vivo* studies are needed to investigate this further (Jung and Schuppe, 2007).

2.10. Mechanism of action of environmental stressors on gamete quality

The effect of environmental stress on gamete quality and reproductive process is now well established. If, however the mechanisms of action of either oxidative stress, EDCs and metabolic disorders are still to be elucidated, several hints on epigenesis and imprinting via perturbation of DNA methylation processes are now increasing. In fact, it has been highlighted that oxidative stress and DNA methylation have as common denominator, i.e. the one carbon cycle, which is a metabolic pathway stimulating the gluthatione synthesis an endogenous antioxidant defense that in turn triggers the recycle of homocysteine, interfering with the methylation process (Dattilo et al., 2016; Menezo et al., 2019; Menezo et al., 2016). Furthermore, in spermiogenesis remodeling, some developmental and imprinted genes maintain their association with histones. In particular, the developmental genes show bivalency, a peculiar epigenetic signature, which is at the basis of embryonic activation. Anomalies related to this epigenetic signature, as DNA methylation irregularity, wrong protamination, or histone modifications, correlate to forms of infertility and reduced embryo development. Since also small noncoding RNAs are kept, and others are actively added to the sperm by affecting normal embryo development it has been suggested that the sperm epigenome may be used to evaluate environmental risk exposure of either the man and the offspring (Carrell, 2019).

3. Conclusions

(1) The impact of environmental deterioration on animal and human reproductive health is now receiving special attention from both scientists and governments all over the world. The huge body of relevant literature shows impressive adverse effects of multifaceted environmental insults on all phases of the reproductive process, from gametogenesis to embryo and fetal development.
(2) This review reports biological consequences of chronic and acute stress factors on the parameters of gamete quality that underpin fertilization competence and developmental outcome.
(3) We have focused on environmental toxicants from a range of agricultural, industrial and medical activities that permeate marine waters, air, soil, consumer food and products, acting mainly as disruptors of endocrine function. Studies *in vitro* and *in vivo* as well as epidemiological data support the concept that both gametes are vulnerable to pollutant exposure, interfering with their fertilizing ability. The majority of studies have been performed on spermatozoa, due to their continuous production in the testes and ease of collection. Far less data are available on oocyte quality, as oocytes are less readily available and are more difficult to assess. Animal models as well as human studies confirm that sperm parameters such as concentration, motility, morphology, viability, mitochondrial activity and genome integrity are affected by metals, antifoulants, organic pollutants, nano-particles and plastics. Emerging environmental changes such as thermal increase and ocean acidification also impair sperm quality. Specific studies demonstrate impairment of plasma membrane electrical characteristics, and oocyte quality seems to be affected in terms of morphological

features such as size, number and maturational stage. These effects in turn have been related to reduced fertilization rate and to the capacity to develop to blastocyst.

(4) Statistics report that almost 15% of couples in the world suffer fertility disorders, and almost 50% of the problems are attributed to male factors. Adverse lifestyle factors together with advanced parental age and delayed childbearing in western countries have a serious detrimental impact on reproductive success (Hart, 2016). Hence, identifying the impact of environmental factors and the mechanisms responsible for their effects on fertility is also relevant in early diagnosis and potential prevention of infertility in couples.

(5) Gametes play a key role in the reproductive scenario, and the prevalence of alarming environmental influences on their quality is under growing scrutiny; to date, clear evidence is still lacking. Recent clues about gamete resilience to environmental stress may account for the capacity of the ecosystem to reorganize and adapt to future change.

(6) More attention to research is needed to validate scientific and clinical findings, in order to: i) further clarify the risk of environmental toxicants and the impact of climate change on modification of gamete physiology and reproductive health; ii) reveal new emerging effects such as alteration of gamete gene expression and transgenerational epigenomic effects; iii) further elucidate mechanisms of action of the environmental stressors, especially those related to ROS production and oxidative stress; iv) utilize all new information in order to promote government intervention for new rules, remedial action, regulation and relevant quality guidelines to protect the global environment.

Acknowledgements

We thank Dr. K. Elder for helpful comments and English revision of the manuscript. Thanks are due to Dr. GL Russo for helpful comments and Mrs Flora Palumbo for art graphic. We apologize with all the colleagues who have contributed to this field for omitting their valuable studies due to editorial space restriction.

ET was supported by Stazione Zoologica institutional funds.

References

Adamkovicova, M., Toman, R., Martiniakova, M., Omelka, R., Babosova, R., Krajcovicova, V., Grosskopf, B., Massanyi, P., 2016. Sperm motility and morphology changes in rats exposed to cadmium and diazinon. Reprod. Biol. Endocrinol. 14, 42.

Adams, J.A., Galloway, T.S., Mondal, D., Esteves, S.C., Mathews, F., 2014. Effect of mobile telephones on sperm quality: A systematic review and meta-analysis. Environ. Int. 70, 106–112.

Adebayo, O.A., Akinloye, O., Adaramoye, O.A., 2018. Cerium oxide nanoparticle elicits oxidative stress, endocrine imbalance and lowers sperm characteristics in testes of balb/c mice. Andrologia 50, e12920.

Adeleye, A.S., Oranu, E.A., Tao, M., Keller, A.A., 2016. Release and detection of nanosized copper from a commercial antifouling paint. Water Res. 102, 374–382.

Agarwal, A., Desai, N.R., Makker, K., Varghese, A., Mouradi, R., Sabanegh, E., Sharma, R., 2009. Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study. Fertil. Steril. 92, 1318–1325.

Airi, V., Gizzi, F., Falini, G., Levy, O., Dubinsky, Z., Goffredo, S., 2014. Reproductive Efficiency of a Mediterranean Endemic Zooxanthellate Coral Decreases with Increasing Temperature along a Wide Latitudinal Gradient. PLoS ONE 9, e91792.

Akcha, F., Spagnol, C., Rouxel, J., 2012. Genotoxicity of diuron and glyphosate in oyster spermatozoa and embryos. Aquat. Toxicol. 106–107, 104–113.

Al-Katanani, Y.M., Paula-Lopes, F.F., Hansen, P.J., 2002. Effect of Season and Exposure to Heat Stress on Oocyte Competence in Holstein Cows. J. Dairy Sci. 85, 390–396.

Allen, J.D., Pechenik, J.A., 2010. Understanding the effects of low salinity on fertilization success and early development in the sand dollar < i > Echinarachnius parma < / i > The Biolog. Bulletin 218, 189–199.

Amara, I., Miled, W., Slama, R.B., Ladhari, N., 2018. Antifouling processes and toxicity effects of antifouling paints on marine environment: A review. Environ. Toxicol. Pharmacol. 57, 115–130.

Ariu, F., Bogliolo, L., Pinna, A., Malfatti, L., Innocenzi, P., Falchi, L., Bebbere, D., Ledda, S., 2017. Cerium oxide nanoparticles (CeO2 NPs) improve the developmental competence of in vitro-matured prepubertal ovine oocytes. Reprod. Fertil. Dev. 29, 1046.

Artimani, T., Amiri, I., Soleimani Asl, S., Saidijam, M., Hasanvand, D., Afshar, S., 2018. Amelioration of diabetes-induced testicular and sperm damage in rats by cerium oxide nanoparticle treatment. Andrologia 50, e13089.

Au, D.W.T., Lee, C.Y., Chan, K.L., Wu, R.S.S., 2001. Reproductive impairment of sea urchins upon chronic exposure to cadmium. Part I: effects on gamete quality. Environ. Pollut. 111, 1–9.

Auta, H.S., Emenike, C.U., Fauziah, S.H., 2017. Distribution and importance of microplastics in the marine environment: a review of the sources, fate, effects, and potential solutions. Environ. Int. 102, 165–176.

Avendaño, C., Mata, A., Sanchez Sarmiento, C.A., Doncel, G.F., 2012. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertil. Steril. 97, 39–45.e2.

Baker, T.J., Tyler, C.R., Galloway, T.S., 2014. Impacts of metal and metal oxide nanoparticles on marine organisms. Environ. Pollut. 186, 257–271.

Barbato, V., Talevi, R., Braun, S., Merolla, A., Sudhakaran, S., Longobardi, S., Gualtieri, R., 2017. Supplementation of sperm media with zinc, D-aspartate and co-enzyme Q10 protects bull sperm against exogenous oxidative stress and improves their ability to support embryo development. Zygote 25, 168–175.

Barkhordari, A., Hekmatimoghaddam, S., Jebali, A., Khalili, M.A., Talebi, A., Noorani, M., 2013. Effect of zinc oxide nanoparticles on viability of human spermatozoa. Iranian J. Reprod. Med. 11, 767.

Bergamo, P., Andreassi, M.G., Lorenzetti, S., 2018. The role of human semen as an early and reliable tool of environmental impact assessment. Spermatozoa InTech, pp. 174–202.

Bergamo, P., Volpe, M.G., Lorenzetti, S., Mantovani, A., Notari, T., Cocca, E., Cerullo, S., Di Stasio, M., Cerino, P., Montano, L., 2016. Human semen as an early, sensitive biomarker of highly polluted living environment in healthy men: a pilot biomonitoring study on trace elements in blood and semen and their relationship with sperm quality and RedOx status. Reprod. Toxicol. 66, 1–9.

Bisht, S., Dada, R., 2017. Oxidative stress: Major executioner in disease pathology, role in sperm DNA damage and preventive strategies. Front Biosci (Schol Ed) 9, 420–447.

Bobe, J., Labbé, C., 2010. Egg and sperm quality in fish. Gen. Comp. Endocrinol. 165, 535–548.

Bondarenko, O., Juganson, K., Ivask, A., Kasemets, K., Mortimer, M., Kahru, A., 2013. Toxicity of Ag, CuO and ZnO nanoparticles to selected environmentally relevant test organisms and mammalian cells in vitro: a critical review. Arch. Toxicol. 87, 1181–1200.

Boni, R., 2019. Heat stress, a serious threat to reproductive function in animals and humans: BONI. Mol. Reprod. Dev.

Boni, R., Gallo, A., Montanino, M., Macina, A., Tosti, E., 2016. Dynamic changes in the sperm quality of *Mytilus galloprovincialis* under continuous thermal stress. Mol. Reprod. Dev. 83, 162–173.

Borges, E., Braga, D.P.D.A.F., Provenza, R.R., Figueira, R.D.C.S., Iaconelli, A., Setti, A.S., 2018. Paternal lifestyle factors in relation to semen quality and in vitro reproductive outcomes. Andrologia 50, e13090.

Brohi, R.D., Wang, L., Talpur, H.S., Wu, D., Khan, F.A., Bhattarai, D., Rehman, Z.-U., Farmanullah, F., Huo, L.-J., 2017. Toxicity of nanoparticles on the reproductive system in animal models: a review. Front. Pharmacol. 8, 606.

Budani, M.C., Tiboni, G.M., 2017. Ovotoxicity of cigarette smoke: A systematic review of the literature. Reprod. Toxicol. 72, 164–181.

Budhwar, S., Singh, V., Verma, P., Singh, K., 2017. Fertilization failure and gamete health: Is there a link? Front. Biosci. (Scholar edition) 9, 395–419.

Bundhun, P.K., Janoo, G., Bhurtu, A., Teeluck, A.R., Soogund, M.Z.S., Pursun, M., Huang, F., 2019. Tobacco smoking and semen quality in infertile males: a systematic review and meta-analysis. BMC Public Health 19, 36.

Byrne, M., Soars, N., Selvakumaraswamy, P., Dworjanyn, S.A., Davis, A.R., 2010. Sea urchin fertilization in a warm, acidified and high pCO2 ocean across a range of sperm densities. Marine Environ. Res. 69, 234–239.

Cai, W., Ji, Y., Song, X., Guo, H., Han, L., Zhang, F., Liu, X., Zhang, H., Zhu, B., Xu, M., 2017. Effects of glyphosate exposure on sperm concentration in rodents: A systematic review and meta-analysis. Environ. Toxicol. Pharmacol. 55, 148–155.

Calogero, A., Polosa, R., Perdichizzi, A., Guarino, F., Vignera, S.L., Scarfia, A., Fratantonio, E., Condorelli, R., Bonanno, O., Barone, N., Burrello, N., D'Agata, R., Vicari, E., 2009. Cigarette smoke extract immobilizes human spermatozoa and induces sperm apoptosis. Reprod. BioMed. Online 19, 564–571.

Campbell, A.L., Ellis, R.P., Urbina, M.A., Mourabit, S., Galloway, T.S., Lewis, C., 2017. Impacts of ocean acidification on sperm develop with exposure time for a polychaete with long lived sperm. Marine Environ. Res. 129, 268–276.

Campbell, A.L., Levitan, D.R., Hosken, D.J., Lewis, C., 2016. Ocean acidification changes the male fitness landscape. Sci. Rep. 6, 31250.

Carnevali, O., Santangeli, S., Forner-Piquer, I., Basili, D., Maradonna, F., 2018. Endocrine-disrupting chemicals in aquatic environment: what are the risks for fish gametes? Fish Physiol. Biochem. 44, 1561–1576.

Carré, J., Gatimel, N., Moreau, J., Parinaud, J., Léandri, R., 2017. Does air pollution play a role in infertility?: a systematic review. Environ. Health 16, 82.

Carrell, D.T., 2019. The Sperm Epigenome: Implications for Assisted Reproductive Technologies. In: Baldi, E., Muratori, M. (Eds.), Genetic Damage in Human Spermatozoa. Springer International Publishing, Cham, pp. 47–56.

Ceyca, J.P., Castillo-Guerrero, J.A., García-Hernández, J., Fernández, G., Betancourt-Lozano, M., 2016. Local and interannual variations in mercury and cadmium in eggs of eight seabird species of the Sinaloa coast, México: Hg and Cd in eggs of seabirds from Sinaloa, México. Environ. Toxicol. Chem. 35, 2330–2338.

Chen, S.X., Yang, X.Z., Deng, Y., Huang, J., Li, Y., Sun, Q., Yu, C.-P., Zhu, Y., Hong, W.S., 2017. Silver nanoparticles induce oocyte maturation in zebrafish (Danio rerio). Chemosphere 170, 51–60.

Chianese, R., Troisi, J., Richards, S., Scafuro, M., Fasano, S., Guida, M., Pierantoni, R., Meccariello, R., 2017. Bisphenol A in reproduction: epigenetic effects. Curr. Med. Chem. 24.

Courbiere, B., Auffan, M., Rollais, R., Tassistro, V., Bonnefoy, A., Botta, A., Rose, J., Orsière, T., Perrin, J., 2013. Ultrastructural interactions and genotoxicity assay of cerium dioxide nanoparticles on mouse oocytes. Int. J. Mol. Sci. 14, 21613–21628.
Dale, B., Wilding, M., Coppola, G., Tosti, E., 2010. How do spermatozoa activate oocytes? Reprod. BioMed. Online 21, 1–3.
Dattilo, M., Giuseppe, D.A., Ettore, C., Ménézo, Y., 2016. Improvement of gamete quality by stimulating and feeding the endogenous antioxidant system: mechanisms, clinical results, insights on gene-environment interactions and the role of diet. J. Assist. Reprod. Genet. 33, 1633–1648.
De Guglielmo, V., Puoti, R., Notariale, R., Maresca, V., Ausió, J., Troisi, J., Verrillo, M., Basile, A., Febbraio, F., Piscopo, M., 2019. Alterations in the properties of sperm protamine-like II protein after exposure of Mytilus galloprovincialis (Lamarck 1819) to sub-toxic doses of cadmium. Ecotoxicol. Environ. Saf. 169, 600–606.
De Iuliis, G.N., Newey, R.J., King, B.V., Aitken, R.J., 2009. Mobile phone radiation induces reactive oxygen species production and dna damage in human spermatozoa in vitro. PLoS ONE 4, e6446.
De, K., Kumar, D., Balaganur, K., Kumar Saxena, V., Thirumurugan, P., Khursheed Naqvi, S.M., 2017. Effect of thermal exposure on physiological adaptability and seminal attributes of rams under semi-arid environment. J. Therm. Biol 65, 113–118.
Dechanet, C., Anahory, T., Mathieu Daude, J.C., Quantin, X., Reyftmann, L., Hamamah, S., Hedon, B., Dechaud, H., 2011. Effects of cigarette smoking on reproduction. Human Reprod. Update 17, 76–95.
Drobnis, E.Z., Nangia, A.K., 2017. Pain medications and male reproduction. In: Impacts of medications on male fertility. Springer International Publishing, Cham, pp. 39–57.
Durack, P.J., Wijffels, S.E., Matear, R.J., 2012. Ocean salinities reveal strong global water cycle intensification during 1950 to 2000. Science 336, 455–458.
Duty, S.M., Silva, M.J., Barr, D.B., Brock, J.W., Ryan, L., Chen, Z., Herrick, R.F., Christiani, D.C., Hauser, R., 2003. Phthalate exposure and human semen parameters. Epidemiology 14, 269–277.
Edwards, J.L., Saxton, A.M., Lawrence, J.L., Payton, R.R., Dunlap, J.R., 2005. Exposure to a physiologically relevant elevated temperature hastens in vitro maturation in bovine oocytes. J. Dairy Sci. 88, 4326–4333.
Esposito, M.C., Boni, R., Cuccaro, A., Tosti, E., Gallo, A., 2020. Sperm motility impairment in free spawning invertebrates under near-future level of ocean acidification: uncovering the mechanism. Front. Marine Sci.
Evenson, D.P., Wixon, R., 2008. Data analysis of two in vivo fertility studies using Sperm Chromatin Structure Assay–derived DNA fragmentation index vs. pregnancy outcome. Fertil. Steril. 90, 1229–1231.
Falchi, L., Galleri, G., Dore, G.M., Zedda, M.T., Pau, S., Bogliolo, L., Ariu, F., Pinna, A., Nieddu, S., Innocenzi, P., Ledda, S., 2018. Effect of exposure to CeO2 nanoparticles on ram spermatozoa during storage at 4 °C for 96 hours. Reprod. Biol. Endocrinol. 16, 19.
Falchuk, K.H., Montorzi, M., 2001. Zinc physiology and biochemistry in oocytes and embryos. Biometals 14, 385–395.
Fathi, N., Hoseinipanah, S.M., Alizadeh, Z., Assari, M.J., Moghimbeigi, A., Mortazavi, M., Haji Hosseini, M., bahmanzadeh, m., 2018. The effect of silver nanoparticleson the reproductive system of adult male rats: A morphological, histological and DNA integrity study. Adv. Clin. Experim. Med. 28, 299–305.
Ferreira, R.M., Ayres, H., Chiaratti, M.R., Ferraz, M.L., Araújo, A.B., Rodrigues, C.A., Watanabe, Y.F., Vireque, A.A., Joaquim, D.C., Smith, L.C., Meirelles, F.V., Baruselli, P.S., 2011. The low fertility of repeat-breeder cows during summer heat stress is related to a low oocyte competence to develop into blastocysts. J. Dairy Sci. 94, 2383–2392.
Ferreira, R.M., Chiaratti, M.R., Macabelli, C.H., Rodrigues, C.A., Ferraz, M.L., Watanabe, Y.F., Smith, L.C., Meirelles, F.V., Baruselli, P.S., 2016. The infertility of repeat-breeder cows during summer is associated with decreased mitochondrial DNA and increased expression of mitochondrial and apoptotic genes in oocytes1. Biol. Reprod. 94.
Foo, S.A., Byrne, M., 2017. Marine gametes in a changing ocean: Impacts of climate change stressors on fecundity and the egg. Marine Environ. Res. 128, 12–24.
Foo, S.A., Deaker, D., Byrne, M., 2018. Cherchez la femme – impact of ocean acidification on the egg jelly coat and attractants for sperm. J. Experim. Biol. 221, jeb177188.
Franchet, C., Goudeau, M., Goudeau, H., 1998. Tributyltin impedes early sperm-egg interactions at the egg coat level in the ascidian Phallusia mammillata but does not prevent sperm-egg fusion in naked eggs. Aquat. Toxicol. 44, 213–228.
Francou, M.M., Girela, J.L., Juan, A.d., Ten Morro, J., Bernabeu, R., Herrero, J., 2017. Human sperm motility, capacitation and acrosome reaction are impaired by 2-arachidonoylglycerol endocannabinoid.
Frumkin, H., Haines, A., 2019. Global environmental change and noncommunicable disease risks. Annu. Rev. Public Health 40, 261–282.
Gallo, A., 2018. Toxicity of marine pollutants on the ascidian oocyte physiology: an electrophysiological approach. Zygote 26, 14–23.
Gallo, A., Boni, R., Buia, M.C., Monfrecola, V., Esposito, M.C., Tosti, E., 2019. Ocean acidification impact on ascidian Ciona robusta spermatozoa: New evidence for stress resilience. Sci. Total Environ. 697, 134100.
Gallo, A., Boni, R., Buttino, I., Tosti, E., 2016. Spermiotoxicity of nickel nanoparticles in the marine invertebrate *Ciona intestinalis* (ascidians). Nanotoxicology 10, 1096–1104.
Gallo, A., Manfra, L., Boni, R., Rotini, A., Migliore, L., Tosti, E., 2018. Cytotoxicity and genotoxicity of CuO nanoparticles in sea urchin spermatozoa through oxidative stress. Environ. Int. 118, 325–333.
Gallo, A., Silvestre, F., Cuomo, A., Papoff, F., Tosti, E., 2011. The impact of metals on the reproductive mechanisms of the ascidian Ciona intestinalis: Metals and reproduction. Mar. Ecol. 32, 222–231.
Gallo, A., Tosti, E., 2013. Adverse effect of antifouling compounds on the reproductive mechanisms of the ascidian ciona intestinalis. Mar. Drugs 11, 3554–3568.
Gallo, A., Tosti, E., 2015. Reprotoxicity of the antifoulant chlorothalonil in ascidians: an ecological risk assessment. PLoS ONE 10, e0123074.
Gambardella, C., Aluigi, M.G., Ferrando, S., Gallus, L., Ramoino, P., Gatti, A.M., Rottigni, M., Falugi, C., 2013. Developmental abnormalities and changes in cholinesterase activity in sea urchin embryos and larvae from sperm exposed to engineered nanoparticles. Aquat. Toxicol. 130–131, 77–85.
Gardon, T., Reisser, C., Soyez, C., Quillien, V., Le Moullac, G., 2018. Microplastics affect energy balance and gametogenesis in the pearl oyster pinctada margaritifera. Environ. Sci. Technol. 52, 5277–5286.
Garolla, A., Torino, M., Sartini, B., Cosci, I., Patassini, C., Carraro, U., Foresta, C., 2013. Seminal and molecular evidence that sauna exposure affects human spermatogenesis. Hum. Reprod. 28, 877–885.
Gold, H.B., Jung, Y.H., Corces, V.G., 2018. Not just heads and tails: The complexity of the sperm epigenome. J. Biol. Chem. 293, 13815–13820.
González-Fernández, C., Tallec, K., Le Goïc, N., Lambert, C., Soudant, P., Huvet, A., Suquet, M., Berchel, M., Paul-Pont, I., 2018. Cellular responses of Pacific oyster (Crassostrea gigas) gametes exposed in vitro to polystyrene nanoparticles. Chemosphere 208, 764–772.
Gregory, M.R., 1996. Plastic 'scrubbers' in hand cleansers: a further (and minor) source for marine pollution identified. Mar. Pollut. Bull. 32, 867–871.
Gualtieri, R., Boni, R., Tosti, E., Zagami, M., Talevi, R., 2005. Intracellular calcium and protein tyrosine phosphorylation during the release of bovine sperm adhering to the fallopian tube epithelium in vitro. Reproduction 129, 51–60.
Hamerezaee, M., Dehghan, S.F., Golbabaei, F., Fathi, A., Barzegar, L., Heidarnejad, N., 2018. Assessment of semen quality among workers exposed to heat stress: a cross-sectional study in a steel industry. Safety Health Work 9, 232–235.
Han, Z., Jiao, S., Kong, D., Shan, Z., Zhang, X., 2011. Effects of β-endosulfan on the growth and reproduction of zebrafish (Danio rerio). Environ. Toxicol. Chem. 30, 2525–2531.
Hansen, B.W., Drillet, G., Pedersen, M.F., Sjøgreen, K.P., Vismann, B., 2012. Do Acartia tonsa (Dana) eggs regulate their volume and osmolality as salinity changes? J. Comp. Physiol. B. 182, 613–623.
Hart, R.J., 2016. Physiological aspects of female fertility: role of the environment, modern lifestyle, and genetics. Physiol. Rev. 96, 873–909.
Hauser, R., 2006. The environment and male fertility: recent research on emerging chemicals and semen quality. Seminars Reprod. Med. 24, 156–167.
Havenhand, J.N., Buttler, F.-R., Thorndyke, M.C., Williamson, J.E., 2008. Near-future levels of ocean acidification reduce fertilization success in a sea urchin. Curr. Biol. 18, R651–R652.
Hédouin, L., Pilon, R., Puisay, A., 2015. Hyposalinity stress compromises the fertilization of gametes more than the survival of coral larvae. Marine Environ. Res. 104, 1–9.
Hjollund, N.H.I., Storgaard, L., Ernst, E., Bonde, J.P., Olsen, J., 2002. Impact of diurnal scrotal temperature on semen quality. Reprod. Toxicol. 16, 215–221.
Ho, M.A., Price, C., King, C.K., Virtue, P., Byrne, M., 2013. Effects of ocean warming and acidification on fertilization in the Antarctic echinoid Sterechinus neumayeri across a range of sperm concentrations. Marine Environ. Res. 90, 136–141.
Huang, C.-H., Yeh, J.-M., Chan, W.-H., 2018. Hazardous impacts of silver nanoparticles on mouse oocyte maturation and fertilization and fetal development through induction of apoptotic processes. Environ. Toxicol. 33, 1039–1049.
Hunter, R.H.F., López-Gatius, F., López-Albors, O., 2017. Temperature gradients in vivo influence maturing male and female gametes in mammals: evidence from the cow. Reprod. Fertil. Dev. 29, 2301.
Isaac, A.V., Kumari, S., Nair, R., Urs, D.R., Salian, S.R., Kalthur, G., Adiga, S.K., Manikkath, J., Mutalik, S., Sachdev, D., Pasricha, R., 2017. Supplementing zinc oxide nanoparticles to cryopreservation medium minimizes the freeze-thaw-induced damage to spermatozoa. Biochem. Biophys. Res. Commun. 494, 656–662.
Islam, F.U., Jalali, S., Shafqat, M.N., Shah, S.T.A., 2017. Endosulfan is toxic to the reproductive health of male freshwater fish, Cyprinion watsoni. Sci. Nature 104, 104.
Itami, N., Shirasuna, K., Kuwayama, T., Iwata, H., 2018. Short-term heat stress induces mitochondrial degradation and biogenesis and enhances mitochondrial quality in porcine oocytes. J. Therm. Biol. 74, 256–263.
Jamalan, M., Ghaffari, M.A., Hoseinzadeh, P., Hashemitabar, M., Zeinali, M., 2016. Human sperm quality and metal toxicants: protective effects of some flavonoids on male reproductive function. Int. J. Fertility Sterility 10, 215.
Jeng, H.A., Huang, Y.-L., Pan, C.-H., Diawara, N., 2015. Role of low exposure to metals as male reproductive toxicants. Int. J. Environ. Health Res. 25, 405–417.
Ju, J.-C., Jiang, S., Tseng, J.-K., Parks, J.E., Yang, X., 2005. Heat shock reduces developmental competence and alters spindle configuration of bovine oocytes. Theriogenology 64, 1677–1689.
Jung, A., Schuppe, H.C., 2007. Influence of genital heat stress on semen quality in humans. Andrologia 39, 203–215.
Jurewicz, J., Hanke, W., Radwan, M., Bonde, J., 2009. Environmental factors and semen quality. Int. J. Occup. Med. Environ. Health 22.
Kadar, E., Dyson, O., Handy, R.D., Al-Subiai, S.N., 2013. Are reproduction impairments of free spawning marine invertebrates exposed to zero-valent nano-iron associated with dissolution of nanoparticles? Nanotoxicology 7, 135–143.
Kadar, E., Tarran, G.A., Jha, A.N., Al-Subiai, S.N., 2011. Stabilization of Engineered Zero-Valent Nanoiron with Na-Acrylic Copolymer Enhances Spermiotoxicity. Environ. Sci. Technol. 45, 3245–3251.
Kamali, K., Atarod, M., Sarhadi, S., Nikbakht, J., Emami, M., Maghsoudi, R., Salimi, H., Fallahpour, B., Kamali, N., Momtazan, A., Ameli, M., 2017. Effects of electromagnetic waves emitted from 3G + Wi-Fi modems on human semen analysis. Urologia J. 84, 209–214.
Kasperczyk, A., Dobrakowski, M., Czuba, Z.P., Kapka-Skrzypczak, L., Kasperczyk, S., 2016. Environmental exposure to zinc and copper influences sperm quality in fertile males. Ann. Agri. Environ. Med. 23.
Kenfack, A., AkonoNantia, E., Ngoula, F., GuiekepNounamo, A., Kamtchouing, P.,

Tchoumboue, J., 2018. Post exposure effects of propoxur (agricultural pesticide) on male fertility in wistar rat. Iranian J. Toxicol. 12, 21–27.
Kesari, K.K., Agarwal, A., Henkel, R., 2018. Radiations and male fertility. Reprod. Biol. Endocrinol. 16, 118.
Kesari, K.K., Kumar, S., Nirala, J., Siddiqui, M.H., Behari, J., 2013. Biophysical evaluation of radiofrequency electromagnetic field effects on male reproductive pattern. Cell Biochem. Biophys. 65, 85–96.
Kubincová, P., Sychrová, E., Raška, J., Basu, A., Yawer, A., Dydowiczová, A., Babica, P., Sovadinová, I., 2019. Polycyclic aromatic hydrocarbons and endocrine disruption: role of testicular gap junctional intercellular communication and connexins. Toxicolog. Sci.
Kukulka, T., Proskurowski, G., Morét-Ferguson, S., Meyer, D.W., Law, K.L., 2012. The effect of wind mixing on the vertical distribution of buoyant plastic debris: wind effects on plastic marine debris. Geophys. Res. Lett. 39, n/a-n/a.
La Vignera, S., Condorelli, R.A., Vicari, E., D'Agata, R., Calogero, A.E., 2012. Effects of the exposure to mobile phones on male reproduction: a review of the literature. J. Androl. 33, 350–356.
Lafuente, D., Garcia, T., Blanco, J., Sánchez, D.J., Sirvent, J.J., Domingo, J.L., Gómez, M., 2016. Effects of oral exposure to silver nanoparticles on the sperm of rats. Reprod. Toxicol. 60, 133–139.
Lafuente, R., García-Blàquez, N., Jacquemin, B., Checa, M.A., 2016. Outdoor air pollution and sperm quality. Fertil. Steril. 106, 880–896.
Lees-Murdock, D.J., Walsh, C.P., 2008. DNA methylation reprogramming in the germ line. Epigenetics 3, 5–13.
Legendre, M., Alavi, S.M.H., Dzyuba, B., Linhart, O., Prokopchuk, G., Cochet, C., Dugué, R., Cosson, J., 2016. Adaptations of semen characteristics and sperm motility to harsh salinity: extreme situations encountered by the euryhaline tilapia Sarotherodon melanotheron heudelotii (Dumeril, 1859). Theriogenology 86, 1251–1267.
Lenz, R.W., Ball, G.D., Leibfried, M.L., Ax, R.L., First, N.L., 1983. In Vitro Maturation and fertilization of bovine oocytes are temperature-dependent processes1. Biol. Reprod. 29, 173–179.
Lettieri, G., Maione, M., Ranauda, M.A., Mele, E., Piscopo, M., 2019a. Molecular effects on spermatozoa of Mytilus galloprovincialis exposed to hyposaline conditions. Mol. Reprod. Dev. mrd.23141.
Lettieri, G., Mollo, V., Ambrosino, A., Caccavale, F., Troisi, J., Febbraio, F., Piscopo, M., 2019. Molecular effects of copper on the reproductive system of mytilus galloprovincialis. Mol. Reprod. Dev.
Li, N., Hou, Y.-H., Jing, W.-X., Dahms, H.-U., Wang, L., 2016. Quality decline and oxidative damage in sperm of freshwater crab Sinopotamon henanense exposed to lead. Ecotoxicol. Environ. Saf. 130, 193–198.
Li, W., Zhou, X., Liu, B., Dai, J., Song, P., Teng, Y., 2016. Effect of nanoparticles on the survival and development of vitrified porcine GV oocytes. CryoLetters 37, 401–405.
Liu, T., Schmitt, R.W., Li, L., 2018. Global search for autumn-lead sea surface salinity predictors of winter precipitation in Southwestern United States. Geophys. Res. Lett.
Lopes, F.F.D.P., Lima, R., Risolia, P.H.B., Ispada, J., Assumpção, M.E.O., Visintin, J.A., 2012. Heat stress induced alteration in bovine oocytes: functional and cellular aspects. Animal Reprod. 395–403.
Lugowska, K., 2018. The effects of Roundup on gametes and early development of common carp (Cyprinus carpio L). Fish Physiol. Biochem. 44, 1109–1117.
Machtinger, R., Combelles, C.M.H., Missmer, S.A., Correia, K.F., Williams, P., Hauser, R., Racowsky, C., 2013. Bisphenol-A and human oocyte maturation in vitro. Hum. Reprod. 28, 2735–2745.
Mai, Z., Lei, M., Yu, B., Du, H., Liu, J., 2014. The effects of cigarette smoke extract on ovulation, oocyte morphology and ovarian gene expression in mice. PLoS ONE 9, e95945.
Manzo, S., Miglietta, M.L., Rametta, G., Buono, S., Di Francia, G., 2013. Embryotoxicity and spermiotoxicity of nanosized ZnO for Mediterranean sea urchin Paracentrotus lividus. J. Hazard. Mater. 254–255, 1–9.
Maqbool, F., Mostafalou, S., Bahadar, H., Abdollahi, M., 2016. Review of endocrine disorders associated with environmental toxicants and possible involved mechanisms. Life Sci. 145, 265–273.
Marettová, E., Maretta, M., Legáth, J., 2015. Toxic effects of cadmium on testis of birds and mammals: a review. Animal Reprod. Sci. 155, 1–10.
Martino, N.A., Marzano, G., Mangiacotti, M., Miedico, O., Sardanelli, A.M., Gnoni, A., Lacalandra, G.M., Chiaravalle, A.E., Ciani, E., Bogliolo, L., Minervini, F., Pizzi, F., Dell'Aquila, M.E., 2017. Exposure to cadmium during in vitro maturation at environmental nanomolar levels impairs oocyte fertilization through oxidative damage: a large animal model study. Reprod. Toxicol. 69, 132–145.
Mathias, F.T., Romano, R.M., Kizys, M.M.L., Kasamatsu, T., Giannocco, G., Chiamolera, M.I., Dias-da-Silva, M.R., Romano, M.A., 2015. Daily exposure to silver nanoparticles during prepubertal development decreases adult sperm and reproductive parameters. Nanotoxicology 9, 64–70.
Maurer-Jones, M.A., Gunsolus, I.L., Murphy, C.J., Haynes, C.L., 2013. Toxicity of Engineered Nanoparticles in the Environment. Anal. Chem. 85, 3036–3049.
McBirney, M., King, S.E., Pappalardo, M., Houser, E., Unkefer, M., Nilsson, E., Sadler-Riggleman, I., Beck, D., Winchester, P., Skinner, M.K., 2017. Atrazine induced epigenetic transgenerational inheritance of disease, lean phenotype and sperm epimutation pathology biomarkers. PLoS ONE 12, e0184306.
McLaren, J.F., 2012. Infertility evaluation. Obst. Gynecol. Clin. 39, 453–463.
Menezo, Y., Dale, B., Elder, K., 2019. The negative impact of the environment on methylation/epigenetic marking in gametes and embryos: A plea for action to protect the fertility of future generations. Mol. Reprod. Dev.
Menezo, Y.J., Russo, G., Tosti, E., Mouatassim, S.E., Benkhalifa, M., 2007. Expression profile of genes coding for DNA repair in human oocytes using pangenomic microarrays, with a special focus on ROS linked decays. J. Assist. Reprod. Genet. 24, 513–520.
Menezo, Y.J.R., Silvestris, E., Dale, B., Elder, K., 2016. Oxidative stress and alterations in DNA methylation: two sides of the same coin in reproduction. Reprod. BioMed. Online 33, 668–683.
Merhi, Z.O., 2012. Challenging cell phone impact on reproduction: A Review. J. Assist. Reprod. Genet. 29, 293–297.
Migliaccio, O., Castellano, I., Cirino, P., Romano, G., Palumbo, A., 2015. Maternal exposure to cadmium and manganese impairs reproduction and progeny fitness in the sea urchin paracentrotus lividus. PLoS ONE 10, e0131815.
Mínguez-Alarcón, L., Hauser, R., Gaskins, A.J., 2016. Effects of bisphenol A on male and couple reproductive health: a review. Fertil. Steril. 106, 864–870.
Moretti, E., Terzuoli, G., Renieri, T., Iacoponi, F., Castellini, C., Giordano, C., Collodel, G., 2013. In vitro effect of gold and silver nanoparticles on human spermatozoa. Andrologia 45, 392–396.
Mostafa, R.M., Nasrallah, Y.S., Hassan, M.M., Farrag, A.F., Majzoub, A., Agarwal, A., 2018. The effect of cigarette smoking on human seminal parameters, sperm chromatin structure and condensation. Andrologia 50, e12910.
Moulin, L., Catarino, A.I., Claessens, T., Dubois, P., 2011. Effects of seawater acidification on early development of the intertidal sea urchin Paracentrotus lividus (Lamarck 1816). Mar. Pollut. Bull. 62, 48–54.
Múgica, M., Sokolova, I.M., Izagirre, U., Marigómez, I., 2015. Season-dependent effects of elevated temperature on stress biomarkers, energy metabolism and gamete development in mussels. Marine Environ. Res. 103, 1–10.
Muthusami, K., Chinnaswamy, P., 2005. Effect of chronic alcoholism on male fertility hormones and semen quality. Fertil. Steril. 84, 919–924.
Nassan, F.L., Arvizu, M., Mínguez-Alarcón, L., Williams, P.L., Attaman, J., Petrozza, J., Hauser, R., Chavarro, J., Team, E.S., Ford, J.B., Keller, M.G., 2019. Marijuana smoking and markers of testicular function among men from a fertility centre. Hum. Reprod. 34, 715–723.
Nazari, M., Talebi, A.R., Hosseini Sharifabad, M., Abbasi, A., Khoradmehr, A., Danafar, A.H., 2016. Acute and chronic effects of gold nanoparticles on sperm parameters and chromatin structure in Mice. Int. J. Reprod. BioMed. 14, 637–642.
Nazmara, Z., Najafi, M., Rezaei-Mojaz, S., Movahedin, M., Zandiyeh, Z., Shirinbayan, P., Roshanpajouh, M., Asgari, H.R., Lavasani, L.H.J., Koruji, M., 2019. The effect of heroin addiction on human sperm parameters, histone-to-protamine transition, and serum sexual hormone levels. Urol. J.
Nissling, A., Larsson, R., 2018. Population specific sperm production in European flounder Platichthys flesus : Adaptation to salinity at spawning. J. Fish Biol. 93, 47–52.
Oliveira, H., Spanò, M., Guevara, M.A., Santos, T.M., Santos, C., Pereira, M.d.L., 2010. Evaluation of in vivo reproductive toxicity of potassium chromate in male mice. Exp. Toxicol. Pathol. 62, 391–404.
Oliveira, H., Spanò, M., Santos, C., Pereira, M.d.L., 2009. Adverse effects of cadmium exposure on mouse sperm. Reprod. Toxicol. 28, 550–555.
Oliviero, M., Schiavo, S., Dumontet, S., Manzo, S., 2019. DNA damages and offspring quality in sea urchin Paracentrotus lividus sperms exposed to ZnO nanoparticles. Sci. Total Environ. 651, 756–765.
Omran, G.A., Gaber, H.D., Mostafa, N.A.M., Abdel-Gaber, R.M., Salah, E.A., 2018. Potential hazards of bisphenol A exposure to semen quality and sperm DNA integrity among infertile men. Reprod. Toxicol. 81, 188–195.
Pavlaki, M.D., Araújo, M.J., Cardoso, D.N., Silva, A.R.R., Cruz, A., Mendo, S., Soares, A.M.V.M., Calado, R., Loureiro, S., 2016. Ecotoxicity and genotoxicity of cadmium in different marine trophic levels. Environ. Pollut. 215, 203–212.
Pawar, K., Kaul, G., 2014. Toxicity of titanium oxide nanoparticles causes functionality and DNA damage in buffalo (Bubalus bubalis) sperm in vitro. Toxicol. Ind. Health 30, 520–533.
Pereira, R., Sá, R., Barros, A., Sousa, M., 2017. Major regulatory mechanisms involved in sperm motility. Asian J. Androl. 19, 5.
Pimm, S.L., Jenkins, C.N., Abell, R., Brooks, T.M., Gittleman, J.L., Joppa, L.N., Raven, P.H., Roberts, C.M., Sexton, J.O., 2014. The biodiversity of species and their rates of extinction, distribution, and protection. Science 344 1246752 1246752.
Preaubert, L., Courbiere, B., Achard, V., Tassistro, V., Greco, F., Orsiere, T., Bottero, J.-Y., Rose, J., Auffan, M., Perrin, J., 2015. Cerium dioxide nanoparticles affect < i > in vitro < /i > fertilization in mice. Nanotoxicology 1–7.
Préaubert, L., Tassistro, V., Auffan, M., Sari-Minodier, I., Rose, J., Courbiere, B., Perrin, J., 2018. Very low concentration of cerium dioxide nanoparticles induce DNA damage, but no loss of vitality, in human spermatozoa. Toxicol. In Vitro 50, 236–241.
Ricci, E., Al Beitawi, S., Cipriani, S., Candiani, M., Chiaffarino, F., Viganò, P., Noli, S., Parazzini, F., 2017. Semen quality and alcohol intake: a systematic review and meta-analysis. Reprod. BioMed. Online 34, 38–47.
Ritter, K.S.P.S.L., 2002. Sources, pathways, and relative risks of contaminants in surface water and groundwater: a perspective prepared for the walkerton inquiry. J. Toxicol. Environ. Health, Part A 65, 1–142.
Roth, Z., Hansen, P.J., 2005. Disruption of nuclear maturation and rearrangement of cytoskeletal elements in bovine oocytes exposed to heat shock during maturation. Reproduction 129, 235–244.
Rubes, J., Selevan, S.G., Evenson, D.P., Zudova, D., Vozdova, M., Zudova, Z., Robbins, W.A., Perreault, S.D., 2005. Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. Hum. Reprod. 20, 2776–2783.
Ruvolo, G., Fattouh, R.R., Bosco, L., Brucculeri, A.M., Cittadini, E., 2013. New molecular markers for the evaluation of gamete quality. J. Assist. Reprod. Genet. 30, 207–212.
Safarinejad, M.R., Asgari, S.A., Farshi, A., Ghaedi, G., Kolahi, A.A., Iravani, S., Khoshdel, A.R., 2013. The effects of opiate consumption on serum reproductive hormone levels, sperm parameters, seminal plasma antioxidant capacity and sperm DNA integrity. Reprod. Toxicol. 36, 18–23.
Sales, K., Vasudeva, R., Dickinson, M.E., Godwin, J.L., Lumley, A.J., Michalczyk, Ł.,

Hebberecht, L., Thomas, P., Franco, A., Gage, M.J.G., 2018. Experimental heatwaves compromise sperm function and cause transgenerational damage in a model insect. Nat. Commun. 9, 4771.
Sansone, A., Di Dato, C., de Angelis, C., Menafra, D., Pozza, C., Pivonello, R., Isidori, A., Gianfrilli, D., 2018. Smoke, alcohol and drug addiction and male fertility. Reprod. Biol. Endocrinol. 16, 3.
Santos, A., Nascimento, M., e Sá, M.d.O., Bila, D., Neto, B.J., Pereira, R., Vieira, M., 2015. Marine Pollution: The Problematic of Microplastics. Journal of Marine Science. Research & Development 5, 1.
Schagdarsurengin, U., Steger, K., 2016. Epigenetics in male reproduction: effect of paternal diet on sperm quality and offspring health. Nat. Rev. Urol. 13, 584–595.
Schlegel, P., Havenhand, J.N., Gillings, M.R., Williamson, J.E., 2012. Individual variability in reproductive success determines winners and losers under ocean acidification: a case study with sea urchins. PLoS ONE 7, e53118.
Schlegel, P., Havenhand, J.N., Obadia, N., Williamson, J.E., 2014. Sperm swimming in the polychaete Galeolaria caespitosa shows substantial inter-individual variability in response to future ocean acidification. Mar. Pollut. Bull. 78, 213–217.
Sharma, R., Biedenharn, K.R., Fedor, J.M., Agarwal, A., 2013. Lifestyle factors and reproductive health: taking control of your fertility. Reprod. Biol. Endocrinol. 11, 66.
Sharma, R., Harlev, A., Agarwal, A., Esteves, S.C., 2016. Cigarette smoking and semen quality: a new meta-analysis examining the effect of the 2010 World Health Organization laboratory methods for the examination of human semen. Eur. Urol. 70, 635–645.
Shi, W., Han, Y., Guo, C., Zhao, X., Liu, S., Su, W., Wang, Y., Zha, S., Chai, X., Liu, G., 2017. Ocean acidification hampers sperm-egg collisions, gamete fusion, and generation of Ca2+ oscillations of a broadcast spawning bivalve, Tegillarca granosa. Marine Environ. Res. 130, 106–112.
Silveyra, G.R., Silveyra, P., Vatnick, I., Medesani, D.A., Rodríguez, E.M., 2018. Effects of atrazine on vitellogenesis, steroid levels and lipid peroxidation, in female red swamp crayfish Procambarus clarkii. Aquat. Toxicol. 197, 136–142.
Simmonds, N.E., Barber, I., 2016. The effect of salinity on egg development and viability of < i > Schistocephalus solidus < /i > (Cestoda: Diphyllobothriidea). J. Parasitol. 102, 42–46.
Smith, B.S., 1981. Tributyltin compounds induce male characteristics on female mud snailsNassarius obsoletus = Ilyanassa obsoleta. J. Appl. Toxicol. 1, 141–144.
Somers, C.M., 2011. Ambient air pollution exposure and damage to male gametes: human studies and in situ 'sentinel' animal experiments. Syst. Biol. Reprod. Med. 57, 63–71.
Sussarellu, R., Suquet, M., Thomas, Y., Lambert, C., Fabioux, C., Pernet, M.E.J., Le Goïc, N., Quillien, V., Mingant, C., Epelboin, Y., Corporeau, C., Guyomarch, J., Robbens, J., Paul-Pont, I., Soudant, P., Huvet, A., 2016. Oyster reproduction is affected by exposure to polystyrene microplastics. Proc. Natl. Acad. Sci. 113, 2430–2435.
Swan, S.H., 2006. Semen quality in fertile US men in relation to geographical area and pesticide exposure. Int. J. Androl. 29, 62–68.
Talbot, P., Lin, S., 2011. The effect of cigarette smoke on fertilization and pre-implantation development: assessment using animal models, clinical data, and stem cells. Biol. Res. 44, 189–194.
Talebi, A.R., Sarcheshmeh, A.A., Khalili, M.A., Tabibnejad, N., 2011. Effects of ethanol consumption on chromatin condensation and DNA integrity of epididymal spermatozoa in rat. Alcohol 45, 403–409.
Tallec, K., Huvet, A., Di Poi, C., González-Fernández, C., Lambert, C., Petton, B., Le Goïc, N., Berchel, M., Soudant, P., Paul-Pont, I., 2018. Nanoplastics impaired oyster free living stages, gametes and embryos. Environ. Pollut. 242, 1226–1235.
Taylor, U., Barchanski, A., Petersen, S., Kues, W.A., Baulain, U., Gamrad, L., Sajti, L., Barcikowski, S., Rath, D., 2014. Gold nanoparticles interfere with sperm functionality by membrane adsorption without penetration. Nanotoxicology 8, 118–127.
Tiedemann, D., Taylor, U., Rehbock, C., Jakobi, J., Klein, S., Kues, W.A., Barcikowski, S., Rath, D., 2014. Reprotoxicity of gold, silver, and gold–silver alloy nanoparticles on mammalian gametes. Analyst 139, 931–942.
Tomza-Marciniak, A., Stępkowska, P., Kuba, J., Pilarczyk, B., 2018. Effect of bisphenol A on reproductive processes: A review of in vitro, in vivo and epidemiological studies: Effect of BPA on reproductive processes. J. Appl. Toxicol. 38, 51–80.
Tosti, E., 1994. Sperm activation in species with external fertilisation. Zygote 2, 359–361.
Tosti, E., Ménézo, Y., 2016. Gamete activation: basic knowledge and clinical applications. Human Reprod. Update 22, 420–439.
Vecoli, C., Montano, L., Andreassi, M.G., 2016. Environmental pollutants: genetic damage and epigenetic changes in male germ cells. Environ. Sci. Pollut. Res. 23, 23339–23348.
Walsh, B.S., Parratt, S.R., Hoffmann, A.A., Atkinson, D., Snook, R.R., Bretman, A., Price, T.A.R., 2019. The impact of climate change on fertility. Trends Ecol. Evol. 34, 249–259.
Wang, L., Li, Y., Fu, J., Zhen, L., Zhao, N., Yang, Q., Li, S., Li, X., 2016. Cadmium inhibits mouse sperm motility through inducing tyrosine phosphorylation in a specific subset of proteins. Reprod. Toxicol. 63, 96–106.
Wang, E., Huang, Y., Du, Q., Sun, Y., 2017. Silver nanoparticle induced toxicity to human sperm by increasing ROS(reactive oxygen species) production and DNA damage. Environ. Toxicol. Pharmacol. 52, 193–199.
Wang, X., Jiang, S.-W., Wang, L., Sun, Y., Xu, F., He, H., Wang, S., Zhang, Z., Pan, X., 2018. Interfering effects of bisphenol A on in vitro growth of preantral follicles and maturation of oocyes. Clin. Chim. Acta 485, 119–125.
Wang, Y.-X., Wang, P., Feng, W., Liu, C., Yang, P., Chen, Y.-J., Sun, L., Sun, Y., Yue, J., Gu, L.-J., Zeng, Q., Lu, W.-Q., 2017. Relationships between seminal plasma metals/metalloids and semen quality, sperm apoptosis and DNA integrity. Environ. Pollut. 224, 224–234.
Weissig, V., Pettinger, T., Murdock, N., 2014. Nanopharmaceuticals (part 1): products on the market. Int. J. Nanomed. 4357.
WHO, 2010. WHO laboratory manual for the examination and processing of human semen.
Wirth, J.J., Rossano, M.G., Potter, R., Puscheck, E., Daly, D.C., Paneth, N., Krawetz, S.A., Protas, B.M., Diamond, M.P., 2008. A pilot study associating urinary concentrations of phthalate metabolites and semen quality. Syst. Biol. Reprod. Med. 54, 143–154.
Wiwanitkit, V., Sereemaspun, A., Rojanathanes, R., 2009. Effect of gold nanoparticles on spermatozoa: the first world report. Fertil. Steril. 91, e7–e8.
Wright, C., Milne, S., Leeson, H., 2014. Sperm DNA damage caused by oxidative stress: modifiable clinical, lifestyle and nutritional factors in male infertility. Reprod. BioMed. Online 28, 684–703.
Wurl, O., Obbard, J.P., 2004. A review of pollutants in the sea-surface microlayer (SML): a unique habitat for marine organisms. Mar. Pollut. Bull. 48, 1016–1030.
Xie, F., Chen, X., Weng, S., Xia, T., Sun, X., Luo, T., Li, P., 2019. Effects of two environmental endocrine disruptors di-n-butyl phthalate (DBP) and mono-n-butyl phthalate (MBP) on human sperm functions in vitro. Reprod. Toxicol. 83, 1–7.
Xu, B., Wang, Z.-P., Wang, Y.-J., Lu, P.-H., Wang, L.-J., Wang, X.-H., 2013. The toxic effect of opioid analgesics on human sperm motility in vitro. Drug Chem. Toxicol. 36, 205–208.
Yoisungnern, T., Choi, Y.-J., Woong Han, J., Kang, M.-H., Das, J., Gurunathan, S., Kwon, D.-N., Cho, S.-G., Park, C., Kyung Chang, W., Chang, B.-S., Parnpai, R., Kim, J.-H., 2015. Internalization of silver nanoparticles into mouse spermatozoa results in poor fertilization and compromised embryo development. Sci. Rep. 5, 11170.
Zarrintab, M., Mirzaei, R., 2017. Stress induced by heavy metals on breeding of magpie (Pica pica) from central Iran. Ecotoxicol. Environ. Saf. 143, 28–37.
Zenzes, M.T., 2000. Smoking and reproduction: gene damage to human gametes and embryos. Human Reprod. Update 6, 122–131.
Zhang, Z.-W., Zhi, G., Qiao, N., Kang, Z.-L., Chen, Z.-L., Hu, L.-M., Yang, Z.-M., Li, Y., 2016. Copper-Induced Spermatozoa Head Malformation Is Related to Oxidative Damage to Testes in CD-1 Mice. Biol. Trace Elem. Res. 173, 427–432.
Zhao, L.-L., Ru, Y.-F., Liu, M., Tang, J.-N., Zheng, J.-F., Wu, B., Gu, Y.-H., Shi, H.-J., 2017. Reproductive effects of cadmium on sperm function and early embryonic development in vitro. PLoS ONE 12, e0186727.