Evolutionary consequences of environmental effects on gamete performance

Angela J. Crean[1,*] and Simone Immler[2]

[1] Charles Perkins Centre, School of Life and Environmental Sciences, The University of Sydney, Sydney NSW 2006, Australia

[2] School of Biological Sciences, University of East Anglia, NR4 7TJ Norwich, UK

* angela.crean@sydney.edu.au ORCID 0000-0003-2605-6435

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Summary

Variation in pre- and post-release gamete environments can influence evolutionary processes by altering fertilisation outcomes and offspring traits. It is now widely accepted that offspring inherit epigenetic information from both their mothers and fathers. Genetic and epigenetic alterations to eggs and sperm acquired post-release may also persist post-fertilisation with consequences for offspring developmental success and later-life fitness. In externally fertilising species, gametes are directly exposed to anthropogenically-induced environmental impacts including pollution, ocean acidification, and climate change. When fertilisation occurs within the female reproductive tract, although gametes are at least partially protected from external environmental variation, the selective environment is likely to vary among females. In both scenarios, gamete traits and selection on gametes can be influenced by environmental conditions such as temperature and pollution as well as intrinsic factors such as male and female reproductive fluids, which may be altered by changes in male and female health and physiology. Here, we highlight some of the pathways through which changes in gamete environments can affect fertilisation dynamics, gamete interactions, and ultimately offspring fitness. We hope that by drawing attention to this important yet often overlooked source of variation we will inspire future research into the evolutionary implications of anthropogenic interference of gamete environments including the use of Assisted Reproductive Technologies.

Environmental effects on gamete phenotypes

In a rapidly changing world, understanding the impact of environmental variation on organisms at all stages is key to predicting population responses to environmental change [1]. Climate change and anthropogenic influence have led to drastic changes and fluctuations in factors including temperature, oxygen levels, pollutants and spatial restrictions [2-5]. Much of our focus on understanding the impact of environmental variation has been centred on the ecosystem, species and population-wide impacts. This approach includes all life stages, but it has become clear that some life stages are more sensitive to environmental change than others [1, 6, 7]. Gametes are susceptible to environmental stress, which is of concern because impacts on reproduction have critical implications for individual fitness which in turn might have ramifications for population health and viability [8, 9].

Environmental variation may affect gametes at two stages: pre-release during oogenesis and spermatogenesis and post-release after ovulation or ejaculation [10]. Environmentally-induced modifications to eggs and sperm acquired pre-release have been the focus of the majority of research into intergenerational and transgenerational epigenetic inheritance in animals (recently reviewed in [11, 12]). Hence, here we largely focus on evolutionary consequences of variation in post-release gamete environments. In this context, external fertilising and sperm-casting (sperm are released into the environment to be subsequently collected by females) species may be particularly vulnerable to environmental change as gametes and early life-history stages are directly exposed to areal (e.g. fungi, plants) or aquatic (e.g. fish) environments [13, 14]. Nevertheless, even if gametes of internal fertilisers are not directly exposed to environmental change, they may be indirectly affected by environmentally-induced changes in both male and female reproductive fluids [15, 16]. Irrespective of fertilisation mode, environmental conditions encountered by gametes after release prior to fertilisation may affect them in two ways: varying environmental conditions may select among gametes and favour some over others (which will be particularly important for male gametes), and/or they may alter the molecular and structural content of the gametes (affecting their function and potentially the fitness of the sired offspring). Both of these impacts have potential evolutionary consequences.

Sperm are the main functional unit of male reproduction, and have therefore been the focus of attention in studies of paternal effects (e.g. [17, 18]). However, males do not just transfer sperm during mating, they transfer an ejaculate. In humans, sperm only constitute about 2 - 5% of the total semen volume. The remainder of the ejaculate – known as seminal plasma or seminal fluid –

contains a complex blend of chemicals (such as proteins, hormones and RNAs) with diverse functions that extend far beyond the simple nourishment of sperm [19-21]. The composition of seminal plasma varies not only among species [22], but also among males and ejaculates within a male [23-25], demonstrating that semen composition is susceptible to environmental change. We know that variation in seminal plasma can regulate sperm phenotype because seminal plasma supplementation can be used to shift sperm traits such that they resemble the sperm traits of the donor ejaculate [26, 27].

Similarly, female reproductive fluids (including ovarian fluid, follicular fluid, cervical mucus, and egg jelly) can influence both gamete phenotypes and interactions between sperm and eggs [28-31]. The role of female reproductive fluids in chemotaxis to lead specific sperm cohorts to the eggs has been described first in broadcast-spawning marine invertebrates [32], but different forms of chemotaxis are also found in other taxa including fish [33-35] and internal fertilisers such as mammals [36]. Female reproductive fluid composition varies among individuals [37, 38], and can affect sperm motility and velocity as well as fertilisation dynamics [39-41]. The composition of the female reproductive fluid may be influenced by female condition [42], and is therefore likely to be similarly influenced by other environmental factors, with consequences for fertilisation success and offspring fitness.

Intergenerational effects of variation in the gamete environment

Adaptive plasticity, in particular maternal and paternal effects, may provide some protection if parents can prepare gametes and offspring for altered conditions [43, 44]. However, parental effects are not necessarily adaptive, and epigenetic inheritance may also amplify negative consequences of environmental change if parents transmit stress to future generations [45, 46]. Furthermore, the fitness consequences of epigenetic changes may not act in the same direction in all life-history stages. For example, increases in sperm fertilisation success may come at a cost to offspring developmental success [47, 48]. Hence, epigenetic inheritance may dampen, amplify, decelerate, or accelerate population responses to environmental change [43, 45].

Environmental conditions may affect gamete performance and molecular structure [49], and these changes can be induced either pre- and/or post-release [10]. Changes in the environment may affect gamete traits such as motility, swimming velocity, morphology and longevity in male gametes [50-53], and size, composition, and structure of female gametes [54-56]. The molecular content of gametes may be affected by the environment through direct DNA damage, RNA and protein decay

[57, 58] as well as changes in the hormonal content in eggs [59]. All these changes may either be triggered by the physiological response to changing environments in the organisms and the soma-germline signalling pathways or through interactions with the intrinsic (seminal and ovarian fluid, female tract etc.) and extrinsic factors (temperature, salinity, pH, toxins etc.) after gamete release. Any of these changes in the gametes have the potential to affect the offspring sired by these gametes [18, 60].

Post-release gamete environments can also have direct effects on the epigenetic content of sperm and eggs [11, 18, 58], again with either adaptive or non-adaptive consequences for fertilisation success and offspring fitness. For example, seminal plasma components can bind directly to sperm, and/or interact with both eggs and the female reproductive tract [20, 21]. Consequently, environmentally-acquired variation in seminal plasma can influence the development and phenotypic traits of offspring, even when the offspring are sired by another male [61-63]. While these effects may be at least partially mediated by female responses in internal fertilisers [64], seminal plasma also affects offspring developmental success and swimming performance in externally fertilising fish [65]. This indicates that variation in seminal plasma can have a direct effect on offspring phenotype.

Stressful environmental conditions during fertilisation can impact fitness in both the parental and offspring generations by reducing fecundity and offspring performance [8]. Experiments in externally-fertilising taxa demonstrate that changes in gamete environments can have carry-over effects on offspring traits that are independent of effects of the parental and developmental environment [66-68]. For example, sperm exposure to an elevated temperature pre-fertilisation resulted in reduced offspring size and swimming performance in a salmonid fish (*Coregonus lavaretus*), even though no effects on sperm performance and embryo mortality were detected [67]. The micro-environment that spawned gametes experience can rapidly fluctuate both temporally and spatially, and thus the gamete environment may differ from the parental and developmental environments. It is possible that within-ejaculate and within-clutch variation in gamete phenotypes may act as a bet-hedging strategy to buffer against unpredictable gamete environments [69].

Finally, while the 'optimal' phenotypes of sperm and eggs vary across environments, environmental conditions may also influence how gametes interact. In internal fertilisers, paternal effects may be modulated by female responses [70, 71]. Similarly, mate choice can occur at the gamete level [30, 31, 72]. These interactions between sperm and eggs may be modified by the environment in which

they occur such that poor performers in one environment are the best performers in another environment [67, 73]. Hence, altered gamete environments may indirectly alter population traits via changes in the outcome of sperm competition [29] and gamete compatibility [30, 31]. Consequently, gamete environments may play an important, yet under-appreciated role in shaping population responses to environmental change [9].

Within-ejaculate variation in sperm phenotype

Experiments in external fertilising species using a split-ejaculate design demonstrate that selecting for different subpopulations of sperm within an ejaculate can translate into differences in offspring phenotypes. For example, ascidian (*Styela plicata*) [74] and Atlantic salmon (*Salmo salar*) [75] eggs fertilised by a subpopulation of longer-lived sperm are more likely to develop and survive. The fitness consequences of within-ejaculate variability in sperm longevity can even carry over to grand-offspring [76]. Within-ejaculate variation in thermal tolerance is also linked to variation in offspring performance; fish larvae (*Coregonus lavaretus*) sired by sperm exposed to increased temperatures were smaller and had reduced swimming performance compared to siblings sired by sperm of the same ejaculate maintained at normal temperatures [67]. Within-ejaculate variation may be adaptive, and could potentially serve as a bet-hedging strategy. For example, larvae of an estuarine tubeworm (*Galeolaria gemineoa*) that were sired by sperm exposed to low salinities had poorer developmental success overall, but performed better in low salinity conditions than siblings sired by sperm exposed to normal salinities [68]. Hence, altered sperm environments may select for different sperm phenotypes, with consequences for offspring fitness.

Within-ejaculate variation in sperm phenotypes may be driven by genetic or epigenetic differences, or likely, a combination of both. Decades of intense research on sperm competition, animal breeding, and reproductive medicine were founded on the premise that sperm phenotypes are predominantly determined by testicular gene expression, and hence the diploid genome of the male [77]. However, at least in some cases, male genotype only explains a minor proportion of variation in sperm function [78, 79]. Sperm phenotype is also influenced by mitochondria and the environment [50]. But exciting new evidence suggests that sperm phenotype is at least partially linked to its haploid genetic content. Evidence for haploid selection in animals [80-82], and post-ejaculation protein transcription by sperm [83], has been steadily increasing. Of note, Alavioon et al [76] experimentally demonstrated that sperm from a single ejaculate with different swimming behaviours differed genetically at numerous sites throughout the genome. In addition, a recent study in house mice and primates showed that the sharing of transcripts in haploid spermatids after

meiosis is for many genes incomplete supporting the idea that a large number of genes expressed at this stage are directly linked to the haploid spermatid genome [84]. These findings suggest that the enduring belief that the genetic content of sperm is not expressed needs to be revised. If sperm do express their haploid genome, then sperm carrying different haploid genotypes may respond to changes in their environment in different ways, resulting in haploid gene by environment interactions.

The sperm environment may also influence within-ejaculate variability in non-genetic factors that are transferred to offspring alongside DNA [18, 85-87]. Several non-genetic components are known to be transferred to the egg including additions and modifications of the chromatic structure through methylation and acetylation, several types of small RNAs as well as proteins such as prions. How these components contribute to the development and fitness of the resulting offspring is still largely unknown. The most direct evidence comes from studies in mice where the injection of sperm RNAs independently of sperm induces changes in offspring phenotypes that fully or partially replicate observed paternal effects [88, 89]. One issue with such experimental designs is that the amount of RNA injected into a zygote is likely to be several orders of magnitude larger than the amount present in the sperm and hence the true mechanisms of how sperm RNAs affect offspring are still unclear. The same is true for other aspects, including methylation, as the inheritance of methylation patterns varies markedly across species and may range from largely maternally inherited in mice [57] to largely paternally inherited in zebrafish [90], thereby influencing the relative importance it may play in paternal non-genetic inheritance. In addition, its true function is thought to be anywhere between gene regulation and the silencing of selfish genetic elements and hence, while being non-genetic themselves it may be strongly associated with genomic variation. The molecular mechanisms of paternal non-genetic inheritance are therefore in great need of more detailed investigation.

Anthropogenic interference of gamete environments

Sperm counts are declining at an alarming rate worldwide. In humans, for example, a trend towards lower sperm counts was first observed in 1974 [91], and although still controversial, was convincingly illustrated in a recent comprehensive meta-analysis [92]. Levine *et al* [92] found that average sperm counts in Western countries have decreased by over 50% in the past 40 years, with no signs that the rate of decline is easing. The pace of change indicates an environmental cause, with several environmental factors potentially contributing to the trend [93]. Of particular concern are increased levels of endocrine disrupting chemicals in the environment, which may be impacting

fertility of both human and wildlife populations [9, 94, 95]. Lifestyle factors, including altered diets and increased rates of obesity are also likely to be contributing to the decrease in sperm counts [96], although the relationship between obesity and male fertility is not clear cut [97]. Another important environmental factor is temperature. Although unlikely to explain much variation in human populations, increasing global temperatures are likely to impact fertility in wildlife populations [8]. These multiple environmental stressors on male fertility are likely to exert strong selective pressures potentially altering which males, and which sperm, pass their genes onto future generations [73].

Assisted Reproductive Technologies (ART) offer several treatment options to overcome infertility, including ovulation induction followed by intrauterine insemination (IUI), in vitro fertilisation (IVF), or intracytoplasmic sperm injection (ICSI). All of these medical interventions expose sperm, eggs, and/or embryos to novel and artificial environmental conditions. Compared to spontaneously conceived children, IVF children show modest yet significant increases in fasting glucose levels, fat deposition, and blood pressure, as well as systemic and pulmonary vascular dysfunction [98-100]. Long-term health consequences of these deceptively subtle health disturbances can be severe, particularly when offspring experience stressful conditions themselves. For example, when challenged with a high-fat diet, IVF-conceived mice suffered a 25% reduction in lifespan compared to naturally-conceived controls [101]. The intergenerational impacts of ART altered gamete environments may be particularly severe because ART allows no opportunity for parental effects to pre-adapt gametes to altered environmental conditions. However, ART protocols and media are optimised to minimise this stress.

The impacts of environmental stress on eggs and embryos during ART are widely acknowledged and accepted, and therefore protocols have been optimised to reduce stress during these stages [102]. Less appreciated is the potential for altered sperm environments to also induce epigenetic changes with consequences for developmental success and offspring health. During the development of semen handling protocols, methods were optimised to maximise fertilisation success only. However, there is now compelling evidence that environmentally-acquired traits can be transmitted from sperm to offspring via non-genetic inheritance mechanisms [18, 58, 64] and hence, ART success rates may be improved by optimising semen preparation protocols to balance fertilisation and offspring developmental success. In particular, semen preparation methods can be used to select which sperm within an ejaculate are used to fertilise eggs.

Despite declines in sperm numbers, the average adult human male still produces over 200 million sperm per ejaculate [92]. However, all sperm are not equal, and only a surprisingly small fraction of sperm needs to be functional for a male to be fertile. According to WHO guidelines, an ejaculate is considered as normal fertility with as little as 32% of sperm showing progressive motility and 4% of sperm having normal morphology (strict criteria) [103]. An underappreciated implication of these differing figures is that many sperm with non-normal morphology are able to swim normally, and could potentially successfully fertilise an egg. Even less is known about how phenotypic differences in these fertile sperm relate to variation in offspring. In fact, selecting a subpopulation of sperm by thermotaxis prior to ICSI results in a greater number of high quality mouse embryos compared to ICSI using unselected sperm [104]. Just as average sperm traits are influenced by a male's environment, the amount of variation in sperm traits within an ejaculate can also be influenced by environmental factors [105, 106]. If these differences in sperm traits are associated with differences in offspring traits, then any factor influencing which sperm within an ejaculate fertilises an egg could also influence offspring.

Evolutionary implications of ART

While ART is used in medical science as a treatment for infertility, the predominant use of ART occurs in agriculture and fisheries, where it is used to enhance selective breeding and production efficiencies [107, 108]. In animal industries, ART is often used in fertile animals over multiple generations. Hence, ART induced epigenetic changes transmitted from gametes to offspring could have evolutionary implications for livestock populations. The most common form of ART applied in agriculture is artificial insemination (AI), producing up to 80% of dairy cattle and 90% of breeding sows in developed countries [107]. Semen from an elite stud male can be diluted and frozen, shipped worldwide, and subsequently used to inseminate herds of females quickly and easily. For example, more than 1000 semen doses can be produced from a single bull ejaculate. Even in this minimally invasive procedure, sperm are exposed to oxygen and light, subjected to altered temperatures, altered nutritional environments (via dilution and supplementation with supportive media), handling and shear stress, and potentially pollutants and contaminants [109]. Because these altered environmental conditions may alter genetic and epigenetic sperm content transmitted to offspring, the extensive use of even just a few steps of ART in animal breeding and fisheries has the potential to induce unanticipated and under-appreciated changes to population traits.

The effects of semen preparation methods on sperm DNA fragmentation [110, 111], and the role of sperm DNA fragmentation in ART outcomes [112, 113] have begun to receive research attention. For

example, it is well known that cryopreservation causes both lethal and sub-lethal damage to sperm (including DNA fragmentation, oxidative stress, and reduced mitochondrial function) with functional consequences for sperm and offspring [114]. A recent study in the brown trout *Salmo trutta* showed that the processes involved in cryopreservation have negative effects on offspring growth even after just one generation [115]. Cryopreservation may also induce epigenetic changes in sperm, with early indications suggesting that patterns of DNA methylation and histone modification are impacted and may be transmitted over several generations [116]. An exciting development that may alleviate some of the infertility problems we are currently facing is the recent finding that embryo development is enhanced by 'starving and subsequently rescuing' sperm motility prior to use in *in vitro* fertilisation [117]. Sperm were 'starved' by incubation in media without nutrients until sperm were no longer motile, then motility was 'rescued' by adding energy substrates to the media. This process increased the number of sperm that became hyperactivated, improving both fertilisation success and post-fertilisation developmental success [117]. Embryo development is also enhanced by transient sperm exposure to a calcium ionophore [118], confirming that embryo development can be improved through modifications to sperm incubation media used in ART. It is too early at this stage, however, to fully understand the possible long-term effects of such seemingly positive interventions.

Conclusion and future directions

Our review highlights an important but underappreciated source of genetic and epigenetic variation – environmental variation in post-release gamete environments. Offspring traits can be influenced by changes in environmental conditions experienced by both eggs and sperm via differential fertilisation success, within-ejaculate and within-clutch selection on gamete phenotypes and potentially haploid genotype by environment interactions, and through the inheritance of epigenetic modifications to the molecular content of both eggs and sperm. This review is not intended to be comprehensive, but rather to inspire both applied and fundamental research into the evolutionary consequences of environmental effects on gamete performance. Many of the ideas presented are largely speculative and require further investigation. An obvious knowledge gap is a lack of understanding of the specific molecular changes driving most of the effects described and the functions of altered molecules on both gametes and embryos. In other words, now that we have shown that post-release gamete environments *can* influence offspring traits, we need to move to the next step of understanding *how* these changes are mediated. Of course, different mechanisms are likely to drive different effects, and multiple mechanisms are likely to have additive and interactive effects in most cases [11].

Other fruitful areas for future investigation include the possibility that sperm are not transcriptionally silent, at least in the early spermatid stages [84] and may express their haploid genome. Such selection may not only be subject to directional (purifying or positive) selection, but also balancing selection induced by variation in environmental conditions during fertilisation. New techniques have also been developed to observe sperm interactions within the female reproductive tract [119-121], which may help to unlock some of the processes by which females differentially select sperm from competing males (i.e. cryptic female choice), which until now have remained elusive. Lastly, we encourage further investigation into the effects of different semen preparation techniques in ART on embryo development. Assisted insemination is used extensively in animal production, veterinary medicine, and conservation biology for practical reasons as it is considered to be minimally invasive. However, because sperm are exposed to altered environments, reproduction via assisted insemination has the potential to affect offspring traits. Modification of semen preparation protocols has the potential to improve outcomes in terms of both the number of offspring produced and the health of these offspring.

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