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

1 **Summary**

2 Variation in pre- and post-release gamete environments can influence evolutionary processes by

3 altering fertilisation outcomes and offspring traits. It is now widely accepted that offspring inherit

4 epigenetic information from both their mothers and fathers. Genetic and epigenetic alterations to

5 eggs and sperm acquired post-release may also persist post-fertilisation with consequences for

6 offspring developmental success and later-life fitness. In externally fertilising species, gametes are

7 directly exposed to anthropogenically-induced environmental impacts including pollution, ocean

8 acidification, and climate change. When fertilisation occurs within the female reproductive tract,

9 although gametes are at least partially protected from external environmental variation, the

10 selective environment is likely to vary among females. In both scenarios, gamete traits and selection

11 on gametes can be influenced by environmental conditions such as temperature and pollution as

12 well as intrinsic factors such as male and female reproductive fluids, which may be altered by

13 changes in male and female health and physiology.   Here, we highlight some of the pathways

14 through which changes in gamete environments can affect fertilisation dynamics, gamete

15 interactions, and ultimately offspring fitness. We hope that by drawing attention to this important

16 yet often overlooked source of variation we will inspire future research into the evolutionary

17 implications of anthropogenic interference of gamete environments including the use of Assisted

18 Reproductive Technologies.

19

20

21

22

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 –

57   contains a complex blend of chemicals (such as proteins, hormones and RNAs) with diverse functions

58   that extend far beyond the simple nourishment of sperm [19-21]. The composition of seminal

59   plasma varies not only among species [22], but also among males and ejaculates within a male [23-

60   25], demonstrating that semen composition is susceptible to environmental change. We know that

61   variation in seminal plasma can regulate sperm phenotype because seminal plasma supplementation

62   can be used to shift sperm traits such that they resemble the sperm traits of the donor ejaculate [26,

63   27].

64

65   Similarly, female reproductive fluids (including ovarian fluid, follicular fluid, cervical mucus, and egg

66   jelly) can influence both gamete phenotypes and interactions between sperm and eggs [28-31]. The

67   role of female reproductive fluids in chemotaxis to lead specific sperm cohorts to the eggs has been

68   described first in broadcast-spawning marine invertebrates [32], but different forms of chemotaxis

69   are also found in other taxa including fish [33-35] and internal fertilisers such as mammals [36].

70   Female reproductive fluid composition varies among individuals [37, 38], and can affect sperm

71   motility and velocity as well as fertilisation dynamics [39-41]. The composition of the female

72   reproductive fluid may be influenced by female condition [42], and is therefore likely to be similarly

73   influenced by other environmental factors, with consequences for fertilisation success and offspring

74   fitness.

75

76   **Intergenerational effects of variation in the gamete environment**

77   Adaptive plasticity, in particular maternal and paternal effects, may provide some protection if

78   parents can prepare gametes and offspring for altered conditions [43, 44]. However, parental effects

79   are not necessarily adaptive, and epigenetic inheritance may also amplify negative consequences of

80   environmental change if parents transmit stress to future generations [45, 46]. Furthermore, the

81   fitness consequences of epigenetic changes may not act in the same direction in all life-history

82   stages. For example, increases in sperm fertilisation success may come at a cost to offspring

83   developmental success [47, 48]. Hence, epigenetic inheritance may dampen, amplify, decelerate, or

84   accelerate population responses to environmental change [43, 45].

85

86   Environmental conditions may affect gamete performance and molecular structure [49], and these

87   changes can be induced either pre- and/or post-release [10]. Changes in the environment may affect

88   gamete traits such as motility, swimming velocity, morphology and longevity in male gametes [50-

89   53], and size, composition, and structure of female gametes [54-56]. The molecular content of

90   gametes may be affected by the environment through direct DNA damage, RNA and protein decay

91 [57, 58] as well as changes in the hormonal content in eggs [59]. All these changes may either be

92 triggered by the physiological response to changing environments in the organisms and the soma-

93 germline signalling pathways or through interactions with the intrinsic (seminal and ovarian fluid,

94 female tract etc.) and extrinsic factors (temperature, salinity, pH, toxins etc.) after gamete release.

95 Any of these changes in the gametes have the potential to affect the offspring sired by these

96 gametes [18, 60].

97

98 Post-release gamete environments can also have direct effects on the epigenetic content of sperm

99 and eggs [11, 18, 58], again with either adaptive or non-adaptive consequences for fertilisation

100 success and offspring fitness. For example, seminal plasma components can bind directly to sperm,

101 and/or interact with both eggs and the female reproductive tract [20, 21]. Consequently,

102 environmentally-acquired variation in seminal plasma can influence the development and

103 phenotypic traits of offspring, even when the offspring are sired by another male [61-63]. While

104 these effects may be at least partially mediated by female responses in internal fertilisers [64],

105 seminal plasma also affects offspring developmental success and swimming performance in

106 externally fertilising fish [65]. This indicates that variation in seminal plasma can have a direct effect

107 on offspring phenotype.

108

109 Stressful environmental conditions during fertilisation can impact fitness in both the parental and

110 offspring generations by reducing fecundity and offspring performance [8]. Experiments in

111 externally-fertilising taxa demonstrate that changes in gamete environments can have carry-over

112 effects on offspring traits that are independent of effects of the parental and developmental

113 environment [66-68]. For example, sperm exposure to an elevated temperature pre-fertilisation

114 resulted in reduced offspring size and swimming performance in a salmonid fish (*Coregonus*

115 *lavaretus*), even though no effects on sperm performance and embryo mortality were detected [67].

116 The micro-environment that spawned gametes experience can rapidly fluctuate both temporally and

117 spatially, and thus the gamete environment may differ from the parental and developmental

118 environments. It is possible that within-ejaculate and within-clutch variation in gamete phenotypes

119 may act as a bet-hedging strategy to buffer against unpredictable gamete environments [69].

120

121 Finally, while the 'optimal' phenotypes of sperm and eggs vary across environments, environmental

122 conditions may also influence how gametes interact. In internal fertilisers, paternal effects may be

123 modulated by female responses [70, 71]. Similarly, mate choice can occur at the gamete level [30,

124 31, 72]. These interactions between sperm and eggs may be modified by the environment in which

125   they occur such that poor performers in one environment are the best performers in another

126   environment [67, 73]. Hence, altered gamete environments may indirectly alter population traits via

127   changes in the outcome of sperm competition [29] and gamete compatibility [30, 31]. Consequently,

128   gamete environments may play an important, yet under-appreciated role in shaping population

129   responses to environmental change [9].

130

131   **Within-ejaculate variation in sperm phenotype**

132   Experiments in external fertilising species using a split-ejaculate design demonstrate that selecting

133   for different subpopulations of sperm within an ejaculate can translate into differences in offspring

134   phenotypes. For example, ascidian (*Styela plicata*) [74] and Atlantic salmon (*Salmo salar*) [75] eggs

135   fertilised by a subpopulation of longer-lived sperm are more likely to develop and survive. The

136   fitness consequences of within-ejaculate variability in sperm longevity can even carry over to grand-

137   offspring [76]. Within-ejaculate variation in thermal tolerance is also linked to variation in offspring

138   performance; fish larvae (*Coregonus lavaretus*) sired by sperm exposed to increased temperatures

139   were smaller and had reduced swimming performance compared to siblings sired by sperm of the

140   same ejaculate maintained at normal temperatures [67]. Within-ejaculate variation may be

141   adaptive, and could potentially serve as a bet-hedging strategy. For example, larvae of an estuarine

142   tubeworm (*Galeolaria gemineoa*) that were sired by sperm exposed to low salinities had poorer

143   developmental success overall, but performed better in low salinity conditions than siblings sired by

144   sperm exposed to normal salinities [68]. Hence, altered sperm environments may select for different

145   sperm phenotypes, with consequences for offspring fitness.

146

147   Within-ejaculate variation in sperm phenotypes may be driven by genetic or epigenetic differences,

148   or likely, a combination of both. Decades of intense research on sperm competition, animal

149   breeding, and reproductive medicine were founded on the premise that sperm phenotypes are

150   predominantly determined by testicular gene expression, and hence the diploid genome of the male

151   [77]. However, at least in some cases, male genotype only explains a minor proportion of variation in

152   sperm function [78, 79]. Sperm phenotype is also influenced by mitochondria and the environment

153   [50]. But exciting new evidence suggests that sperm phenotype is at least partially linked to its

154   haploid genetic content. Evidence for haploid selection in animals [80-82], and post-ejaculation

155   protein transcription by sperm [83], has been steadily increasing. Of note, Alavioon et al [76]

156   experimentally demonstrated that sperm from a single ejaculate with different swimming

157   behaviours differed genetically at numerous sites throughout the genome. In addition, a recent

158   study in house mice and primates showed that the sharing of transcripts in haploid spermatids after

159   meiosis is for many genes incomplete supporting the idea that a large number of genes expressed at

160   this stage are directly linked to the haploid spermatid genome [84]. These findings suggest that the

161   enduring belief that the genetic content of sperm is not expressed needs to be revised. If sperm do

162   express their haploid genome, then sperm carrying different haploid genotypes may respond to

163   changes in their environment in different ways, resulting in haploid gene by environment

164   interactions.

165

166   The sperm environment may also influence within-ejaculate variability in non-genetic factors that

167   are transferred to offspring alongside DNA [18, 85-87]. Several non-genetic components are known

168   to be transferred to the egg including additions and modifications of the chromatic structure

169   through methylation and acetylation, several types of small RNAs as well as proteins such as prions.

170   How these components contribute to the development and fitness of the resulting offspring is still

171   largely unknown. The most direct evidence comes from studies in mice where the injection of sperm

172   RNAs independently of sperm induces changes in offspring phenotypes that fully or partially

173   replicate observed paternal effects [88, 89]. One issue with such experimental designs is that the

174   amount of RNA injected into a zygote is likely to be several orders of magnitude larger than the

175   amount present in the sperm and hence the true mechanisms of how sperm RNAs affect offspring

176   are still unclear. The same is true for other aspects, including methylation, as the inheritance of

177   methylation patterns varies markedly across species and may range from largely maternally

178   inherited in mice [57] to largely paternally inherited in zebrafish [90], thereby influencing the relative

179   importance it may play in paternal non-genetic inheritance. In addition, its true function is thought

180   to be anywhere between gene regulation and the silencing of selfish genetic elements and hence,

181   while being non-genetic themselves it may be strongly associated with genomic variation. The

182   molecular mechanisms of paternal non-genetic inheritance are therefore in great need of more

183   detailed investigation.

184

185   **Anthropogenic interference of gamete environments**

186   Sperm counts are declining at an alarming rate worldwide. In humans, for example, a trend towards

187   lower sperm counts was first observed in 1974 [91], and although still controversial, was

188   convincingly illustrated in a recent comprehensive meta-analysis [92]. Levine *et al* [92] found that

189   average sperm counts in Western countries have decreased by over 50% in the past 40 years, with

190   no signs that the rate of decline is easing. The pace of change indicates an environmental cause, with

191   several environmental factors potentially contributing to the trend [93]. Of particular concern are

192   increased levels of endocrine disrupting chemicals in the environment, which may be impacting

193 fertility of both human and wildlife populations [9, 94, 95]. Lifestyle factors, including altered diets

194 and increased rates of obesity are also likely to be contributing to the decrease in sperm counts [96],

195 although the relationship between obesity and male fertility is not clear cut [97]. Another important

196 environmental factor is temperature. Although unlikely to explain much variation in human

197 populations, increasing global temperatures are likely to impact fertility in wildlife populations [8].

198 These multiple environmental stressors on male fertility are likely to exert strong selective pressures

199 potentially altering which males, and which sperm, pass their genes onto future generations [73].

200

201 Assisted Reproductive Technologies (ART) offer several treatment options to overcome infertility,

202 including ovulation induction followed by intrauterine insemination (IUI), in vitro fertilisation (IVF),

203 or intracytoplasmic sperm injection (ICSI). All of these medical interventions expose sperm, eggs,

204 and/or embryos to novel and artificial environmental conditions. Compared to spontaneously

205 conceived children, IVF children show modest yet significant increases in fasting glucose levels, fat

206 deposition, and blood pressure, as well as systemic and pulmonary vascular dysfunction [98-100].

207 Long-term health consequences of these deceptively subtle health disturbances can be severe,

208 particularly when offspring experience stressful conditions themselves. For example, when

209 challenged with a high-fat diet, IVF-conceived mice suffered a 25% reduction in lifespan compared to

210 naturally-conceived controls [101]. The intergenerational impacts of ART altered gamete

211 environments may be particularly severe because ART allows no opportunity for parental effects to

212 pre-adapt gametes to altered environmental conditions. However, ART protocols and media are

213 optimised to minimise this stress.

214

215 The impacts of environmental stress on eggs and embryos during ART are widely acknowledged and

216 accepted, and therefore protocols have been optimised to reduce stress during these stages [102].

217 Less appreciated is the potential for altered sperm environments to also induce epigenetic changes

218 with consequences for developmental success and offspring health. During the development of

219 semen handling protocols, methods were optimised to maximise fertilisation success only. However,

220 there is now compelling evidence that environmentally-acquired traits can be transmitted from

221 sperm to offspring via non-genetic inheritance mechanisms [18, 58, 64] and hence, ART success rates

222 may be improved by optimising semen preparation protocols to balance fertilisation and offspring

223 developmental success. In particular, semen preparation methods can be used to select which

224 sperm within an ejaculate are used to fertilise eggs.

225

226 Despite declines in sperm numbers, the average adult human male still produces over 200 million
227 sperm per ejaculate [92]. However, all sperm are not equal, and only a surprisingly small fraction of
228 sperm needs to be functional for a male to be fertile. According to WHO guidelines, an ejaculate is
229 considered as normal fertility with as little as 32% of sperm showing progressive motility and 4% of
230 sperm having normal morphology (strict criteria) [103]. An underappreciated implication of these
231 differing figures is that many sperm with non-normal morphology are able to swim normally, and
232 could potentially successfully fertilise an egg. Even less is known about how phenotypic differences
233 in these fertile sperm relate to variation in offspring. In fact, selecting a subpopulation of sperm by
234 thermotaxis prior to ICSI results in a greater number of high quality mouse embryos compared to
235 ICSI using unselected sperm [104]. Just as average sperm traits are influenced by a male's
236 environment, the amount of variation in sperm traits within an ejaculate can also be influenced by
237 environmental factors [105, 106]. If these differences in sperm traits are associated with differences
238 in offspring traits, then any factor influencing which sperm within an ejaculate fertilises an egg could
239 also influence offspring.
240
241 **Evolutionary implications of ART**
242 While ART is used in medical science as a treatment for infertility, the predominant use of ART
243 occurs in agriculture and fisheries, where it is used to enhance selective breeding and production
244 efficiencies [107, 108]. In animal industries, ART is often used in fertile animals over multiple
245 generations. Hence, ART induced epigenetic changes transmitted from gametes to offspring could
246 have evolutionary implications for livestock populations. The most common form of ART applied in
247 agriculture is artificial insemination (AI), producing up to 80% of dairy cattle and 90% of breeding
248 sows in developed countries [107]. Semen from an elite stud male can be diluted and frozen,
249 shipped worldwide, and subsequently used to inseminate herds of females quickly and easily. For
250 example, more than 1000 semen doses can be produced from a single bull ejaculate. Even in this
251 minimally invasive procedure, sperm are exposed to oxygen and light, subjected to altered
252 temperatures, altered nutritional environments (via dilution and supplementation with supportive
253 media), handling and shear stress, and potentially pollutants and contaminants [109]. Because these
254 altered environmental conditions may alter genetic and epigenetic sperm content transmitted to
255 offspring, the extensive use of even just a few steps of ART in animal breeding and fisheries has the
256 potential to induce unanticipated and under-appreciated changes to population traits.
257
258 The effects of semen preparation methods on sperm DNA fragmentation [110, 111], and the role of
259 sperm DNA fragmentation in ART outcomes [112, 113] have begun to receive research attention. For

260   example, it is well known that cryopreservation causes both lethal and sub-lethal damage to sperm

261   (including DNA fragmentation, oxidative stress, and reduced mitochondrial function) with functional

262   consequences for sperm and offspring [114]. A recent study in the brown trout *Salmo trutta* showed

263   that the processes involved in cryopreservation have negative effects on offspring growth even after

264   just one generation [115]. Cryopreservation may also induce epigenetic changes in sperm, with early

265   indications suggesting that patterns of DNA methylation and histone modification are impacted and

266   may be transmitted over several generations [116]. An exciting development that may alleviate

267   some of the infertility problems we are currently facing is the recent finding that embryo

268   development is enhanced by 'starving and subsequently rescuing' sperm motility prior to use in *in*

269   *vitro* fertilisation [117]. Sperm were 'starved' by incubation in media without nutrients until sperm

270   were no longer motile, then motility was 'rescued' by adding energy substrates to the media. This

271   process increased the number of sperm that became hyperactivated, improving both fertilisation

272   success and post-fertilisation developmental success [117]. Embryo development is also enhanced

273   by transient sperm exposure to a calcium ionophore [118], confirming that embryo development can

274   be improved through modifications to sperm incubation media used in ART. It is too early at this

275   stage, however, to fully understand the possible long-term effects of such seemingly positive

276   interventions.

277

278   **Conclusion and future directions**

279   Our review highlights an important but underappreciated source of genetic and epigenetic variation

280   – environmental variation in post-release gamete environments. Offspring traits can be influenced

281   by changes in environmental conditions experienced by both eggs and sperm via differential

282   fertilisation success, within-ejaculate and within-clutch selection on gamete phenotypes and

283   potentially haploid genotype by environment interactions, and through the inheritance of epigenetic

284   modifications to the molecular content of both eggs and sperm. This review is not intended to be

285   comprehensive, but rather to inspire both applied and fundamental research into the evolutionary

286   consequences of environmental effects on gamete performance. Many of the ideas presented are

287   largely speculative and require further investigation. An obvious knowledge gap is a lack of

288   understanding of the specific molecular changes driving most of the effects described and the

289   functions of altered molecules on both gametes and embryos. In other words, now that we have

290   shown that post-release gamete environments *can* influence offspring traits, we need to move to

291   the next step of understanding *how* these changes are mediated. Of course, different mechanisms

292   are likely to drive different effects, and multiple mechanisms are likely to have additive and

293   interactive effects in most cases [11].

294

295   Other fruitful areas for future investigation include the possibility that sperm are not

296   transcriptionally silent, at least in the early spermatid stages [84] and may express their haploid

297   genome. Such selection may not only be subject to directional (purifying or positive) selection, but

298   also balancing selection induced by variation in environmental conditions during fertilisation. New

299   techniques have also been developed to observe sperm interactions within the female reproductive

300   tract [119-121], which may help to unlock some of the processes by which females differentially

301   select sperm from competing males (i.e. cryptic female choice), which until now have remained

302   elusive. Lastly, we encourage further investigation into the effects of different semen preparation

303   techniques in ART on embryo development. Assisted insemination is used extensively in animal

304   production, veterinary medicine, and conservation biology for practical reasons as it is considered to

305   be minimally invasive. However, because sperm are exposed to altered environments, reproduction

306   via assisted insemination has the potential to affect offspring traits. Modification of semen

307   preparation protocols has the potential to improve outcomes in terms of both the number of

308   offspring produced and the health of these offspring.

309

310

311   **Acknowledgements**

316

317

318   **References**

319   [1] Donelson, J. M., Salinas, S., Munday, P. L. & Shama, L. N. S. 2018 Transgenerational
320   plasticity and climate change experiments: Where do we go from here? *Glob Chang Biol* **24**,
321   13-34. (DOI:10.1111/gcb.13903).
322   [2] Malhi, Y., Franklin, J., Seddon, N., Solan, M., Turner, M. G., Field, C. B. & Knowlton, N.
323   2020 Climate change and ecosystems: threats, opportunities and solutions. *Phil Trans R Soc*
324   *B* **375**, 20190104. (DOI:10.1098/rstb.2019.0104).
325   [3] Halpern, B. S., Frazier, M., Afflerbach, J., Lowndes, J. S., Micheli, F., O'Hara, C.,
326   Scarborough, C. & Selkoe, K. A. 2019 Recent pace of change in human impact on the world's
327   ocean. *Sci Rep.* **9**, 11609. (DOI:10.1038/s41598-019-47201-9).
328   [4] Sippel, S., Meinshausen, N., Fischer, E. M., Szekely, E. & Knutti, R. 2020 Climate change
329   now detectable from any single day of weather at global scale. *Nat Clim Chang* **10**, 35-41.
330   (DOI:10.1038/s41558-019-0666-7).

331 [5] Kling, M. M., Auer, S. L., Comer, P. J., Ackerly, D. D. & Hamilton, H. 2020 Multiple axes of
332 ecological vulnerability to climate change. *Glob Chang Biol* **26**, 2798-2813.
333 (DOI:10.1111/gcb.15008).
334 [6] Byrne, M. 2011 Impact of ocean warming and ocean acidification on marine invertebrate
335 life history stages: vulnerabilities and potential for persistence in a changing ocean.
336 *Oceanogr Mar Biol* **49**, 1-42.
337 [7] Burton, T. & Metcalfe, N. B. 2014 Can environmental conditions experienced in early life
338 influence future generations? *Proc R Soc B* **281**, 20140311. (DOI:10.1098/rspb.2014.0311).
339 [8] Walsh, B. S., Parratt, S. R., Hoffmann, A. A., Atkinson, D., Snook, R. R., Bretman, A. &
340 Price, T. A. R. 2019 The impact of climate change on fertility. *Trends Ecol Evol* **34**, 249-259.
341 (DOI:10.1016/j.tree.2018.12.002).
342 [9] Aulsebrook, L. C., Bertram, M. G., Martin, J. M., Aulsebrook, A. E., Brodin, T., Evans, J. P.,
343 Hall, M. D., O'Bryan, M. K., Pask, A. J., Tyler, C. R., et al. 2020 Reproduction in a polluted
344 world: implications for wildlife. *Reproduction* **160**, R13-23. (DOI:10.1530/rep-20-0154).
345 [10] Marshall, D. J. 2015 Environmentally induced (co)variance in sperm and offspring
346 phenotypes as a source of epigenetic effects. *J Exp Biol* **218**, 107-113.
347 (DOI:10.1242/jeb.106427).
348 [11] Lempradl, A. 2020 Germ cell-mediated mechanisms of epigenetic inheritance. *Semin*
349 *Cell Dev Biol.* **97**, 116-122. (DOI:10.1016/j.semcdb.2019.07.012).
350 [12] Safi-Stibler, S. & Gabory, A. 2020 Epigenetics and the Developmental Origins of Health
351 and Disease: Parental environment signalling to the epigenome, critical time windows and
352 sculpting the adult phenotype. *Semin Cell Dev Biol.* **97**, 172-180.
353 (DOI:10.1016/j.semcdb.2019.09.008).
354 [13] Albright, R. & Mason, B. 2013 Projected near-future levels of temperature and pCO(2)
355 reduce coral fertilization success. *PloS one* **8**, e56468. (DOI:10.1371/journal.pone.0056468).
356 [14] Keshavmurthy, S., Fontana, S., Mezaki, T., González, L. d. C. & Chen, C. A. 2014 Doors
357 are closing on early development in corals facing climate change. *Sci Rep.* **4**, 5633.
358 (DOI:10.1038/srep05633).
359 [15] Woodruff, T. J., Janssen, S. J., Guillette Jr, L. J. & Giudice, L. C. 2010 *Environmental*
360 *impacts on reproductive health and fertility*. Cambridge, Cambridge University Press.
361 [16] Skakkebaek, N. E., Rajpert-De Meyts, E., Buck Louis, G. M., Toppari, J., Andersson, A. M.,
362 Eisenberg, M. L., Jensen, T. K., Jorgensen, N., Swan, S. H., Sapra, K. J., et al. 2016 Male
363 reproductive disorders and fertility trends: influences of environment and genetic
364 susceptibility. *Physiol Rev.* **96**, 55-97. (DOI:10.1152/physrev.00017.2015).
365 [17] Rando, O. J. 2016 Intergenerational transfer of epigenetic information in sperm. *Cold*
366 *Spring Harb Perspect Med* **6**, a022988. (DOI:10.1101/cshperspect.a022988).
367 [18] Immler, S. 2018 The sperm factor: paternal impact beyond genes. *Heredity* **121**, 239-
368 247. (DOI:10.1038/s41437-018-0111-0).
369 [19] Druart, X. & de Graaf, S. 2018 Seminal plasma proteomes and sperm fertility. *Anim*
370 *Reprod Sci* **194**, 33-40. (DOI:10.1016/j.anireprosci.2018.04.061).
371 [20] Samanta, L., Parida, R., Dias, T. R. & Agarwal, A. 2018 The enigmatic seminal plasma: a
372 proteomics insight from ejaculation to fertilization. *Reprod Biol Endocrin* **16**, 41.
373 (DOI:10.1186/s12958-018-0358-6).
374 [21] Schjenken, J. E. & Robertson, S. A. 2020 The female response to seminal fluid. *Physiol*
375 *Rev.* **100**, 1077-1117. (DOI:10.1152/physrev.00013.2018).
376 [22] Druart, X., Rickard, J. P., Mactier, S., Kohnke, P. L., Kershaw-Young, C. M., Bathgate, R.,
377 Gibb, Z., Crossett, B., Tsikis, G., Labas, V., et al. 2013 Proteomic characterization and cross

species comparison of mammalian seminal plasma. *J Proteomics.* **91**, 13-22. (DOI:10.1016/j.jprot.2013.05.029).

[23] Leahy, T., Marti, J. I., Evans, G. & Maxwell, W. M. 2010 Seasonal variation in the protective effect of seminal plasma on frozen-thawed ram spermatozoa. *Anim Reprod Sci* **119**, 147-153. (DOI:10.1016/j.anireprosci.2009.12.010).

[24] Patlar, B., Weber, M. & Ramm, S. A. 2019 Genetic and environmental variation in transcriptional expression of seminal fluid proteins. *Heredity* **122**, 595-611. (DOI:10.1038/s41437-018-0160-4).

[25] Fraser, L., Strzeżek, J., Filipowicz, K., Mogielnicka-Brzozowska, M. & Zasiadczyk, L. 2016 Age and seasonal-dependent variations in the biochemical composition of boar semen. *Theriogenology* **86**, 806-816. (DOI:10.1016/j.theriogenology.2016.02.035).

[26] Rickard, J. P., Schmidt, R. E., Maddison, J. W., Bathgate, R., Lynch, G. W., Druart, X. & de Graaf, S. P. 2016 Variation in seminal plasma alters the ability of ram spermatozoa to survive cryopreservation. *Reprod Fertil Dev.* **28**, 516-523. (DOI:10.1071/rd14123).

[27] Green, C., Rickard, J. P., de Graaf, S. P. & Crean, A. J. 2020 From one ejaculate to another: transference of sperm traits via seminal plasma supplementation in the ram. *Biology* **9**. (DOI:10.3390/biology9020033).

[28] Zadmajid, V., Myers, J. N., Sørensen, S. R. & Ernest Butts, I. A. 2019 Ovarian fluid and its impacts on spermatozoa performance in fish: a review. *Theriogenology* **132**, 144-152. (DOI:10.1016/j.theriogenology.2019.03.021).

[29] Gasparini, C., Pilastro, A. & Evans, J. P. 2020 The role of female reproductive fluid in sperm competition. *Phil Trans R Soc B* **375**, 20200077.

[30] Fitzpatrick, J. L., Willis, C., Devigili, A., Young, A., Carroll, M., Hunter, H. R. & Brison, D. R. 2020 Chemical signals from eggs facilitate cryptic female choice in humans. *Proc R Soc B* **287**, 20200805. (DOI:10.1098/rspb.2020.0805).

[31] Jokiniemi, A., Magris, M., Ritari, J., Kuusipalo, L., Lundgren, T., Partanen, J. & Kekäläinen, J. 2020 Post-copulatory genetic matchmaking: HLA-dependent effects of cervical mucus on human sperm function. *Proc R Soc B* **287**, 20201682. (DOI:10.1098/rspb.2020.1682).

[32] Evans, J. P., Garcia-Gonzalez, F., Almbro, M., Robinson, O. & Fitzpatrick, J. L. 2012 Assessing the potential for egg chemoattractants to mediate sexual selection in a broadcast spawning marine invertebrate. *Proc R Soc B* **279**, 2855-2861. (DOI:10.1098/rspb.2012.0181).

[33] Yeates, S. E., Diamond, S. E., Einum, S., Emerson, B. C., Holt, W. V. & Gage, M. J. G. 2013 Cryptic choice of conspecific sperm controlled by the impact of ovarian fluid on sperm swimming behavior. *Evolution* **67**, 3523-3536. (DOI:10.1111/evo.12208).

[34] Alonzo, S. H., Stiver, K. A. & Marsh-Rollo, S. E. 2016 Ovarian fluid allows directional cryptic female choice despite external fertilization. *Nat Commun* **7**, 12452. (DOI:10.1038/ncomms12452).

[35] Myers, J. N., Senior, A., Zadmajid, V., Sorensen, S. R. & Butts, I. A. E. 2020 Associations between ovarian fluid and sperm swimming trajectories in marine and freshwater teleosts: A meta-analysis. *Rev Fish Sci Aquac* **28**, 322-339. (DOI:10.1080/23308249.2020.1739623).

[36] Yoshida, M. & Yoshida, K. 2011 Sperm chemotaxis and regulation of flagellar movement by Ca2+. *Mol Hum Reprod* **17**, 457-465. (DOI:10.1093/molehr/gar041).

[37] Johnson, S. L., Villarroel, M., Rosengrave, P., Carne, A., Kleffmann, T., Lokman, P. M. & Gemmell, N. J. 2014 Proteomic analysis of chinook salmon (*Oncorhynchus tshawytscha*) ovarian fluid. *PloS one* **9**, e104155. (DOI:10.1371/journal.pone.0104155).

424 [38] İnanan, B. E. & Öğretmen, F. 2015 Determination of differences in the biochemical
425 properties of sperm activating and non-activating ovarian fluids and their influences on
426 sperm motility in rainbow trout (*Oncorhynchus mykiss*). *Aquaculture* **448**, 539-544.
427 (DOI:10.1016/j.aquaculture.2015.06.018).
428 [39] Poli, F., Immler, S. & Gasparini, C. 2019 Effects of ovarian fluid on sperm traits and its
429 implications for cryptic female choice in zebrafish. *Behav Ecol* **30**, 1298-1305.
430 (DOI:10.1093/beheco/arz077).
431 [40] Lymbery, R. A., Kennington, W. J. & Evans, J. P. 2017 Egg chemoattractants moderate
432 intraspecific sperm competition. *Evol Lett* **1**, 317-327. (DOI:10.1002/evl3.34).
433 [41] Hadlow, J. H., Evans, J. P. & Lymbery, R. A. 2020 Egg-induced changes to sperm
434 phenotypes shape patterns of multivariate selection on ejaculates. *J Evol Biol* **33**, 797-807.
435 (DOI:10.1111/jeb.13611).
436 [42] Cardozo, G. & Pilastro, A. 2018 Female nutritional condition affects ovarian fluid quality
437 in guppies. *Biol Lett* **14**. (DOI:10.1098/rsbl.2018.0122).
438 [43] Munday, P. L., Warner, R. R., Monro, K., Pandolfi, J. M. & Marshall, D. J. 2013 Predicting
439 evolutionary responses to climate change in the sea. *Ecol Lett.* **16**, 1488-1500.
440 (DOI:10.1111/ele.12185).
441 [44] Foo, S. A. & Byrne, M. 2016 Acclimatization and adaptive capacity of marine species in a
442 changing ocean. *Adv Mar Biol.* **74**, 69-116. (DOI:10.1016/bs.amb.2016.06.001).
443 [45] Bonduriansky, R., Crean, A. J. & Day, T. 2012 The implications of nongenetic inheritance
444 for evolution in changing environments. *Evol Appl.* **5**, 192-201. (DOI:10.1111/j.1752-
445 4571.2011.00213.x).
446 [46] Bonduriansky, R. & Crean, A. J. 2018 What are parental condition-transfer effects and
447 how can they be detected? *Methods Ecol Evol* **9**, 450-456. (DOI:10.1111/2041-210x.12848).
448 [47] Crean, A. J., Dwyer, J. M. & Marshall, D. J. 2013 Adaptive paternal effects? Experimental
449 evidence that the paternal environment affects offspring performance. *Ecology* **94**, 2575-
450 2582. (DOI:10.1890/13-0184.1).
451 [48] Kekalainen, J., Soler, C., Veentaus, S. & Huuskonen, H. 2015 Male investments in high
452 quality sperm improve fertilization success, but may have negative impact on offspring
453 fitness in whitefish. *PloS one* **10**, e0137005. (DOI:10.1371/journal.pone.0137005).
454 [49] Gallo, A., Boni, R. & Tosti, E. 2020 Gamete quality in a multistressor environment.
455 *Environ Int* **138**, 105627. (DOI:10.1016/j.envint.2020.105627).
456 [50] Reinhardt, K., Dobler, R. & Abbott, J. 2015 An ecology of sperm: sperm diversification by
457 natural selection. *Annu Rev Ecol Evol S* **46**, 435-459. (DOI:10.1146/annurev-ecolsys-120213-
458 091611).
459 [51] Falkenberg, L. J., Styan, C. A. & Havenhand, J. N. 2019 Sperm motility of oysters from
460 distinct populations differs in response to ocean acidification and freshening. *Sci Rep.* **9**,
461 7970. (DOI:10.1038/s41598-019-44321-0).
462 [52] Fenkes, M., Fitzpatrick, J. L., Ozolina, K., Shiels, H. A. & Nudds, R. L. 2017 Sperm in hot
463 water: direct and indirect thermal challenges interact to impact on brown trout sperm
464 quality. *J Exp Biol* **220**, 2513. (DOI:10.1242/jeb.156018).
465 [53] Chirgwin, E., Marshall, D. J. & Monro, K. 2020 Physical and physiological impacts of
466 ocean warming alter phenotypic selection on sperm morphology. *Funct Ecol* **34**, 646-657.
467 (DOI:10.1111/1365-2435.13483).
468 [54] Krisher, R. L. 2013 In vivo and in vitro environmental effects on mammalian oocyte
469 quality. *Annu Rev Anim Biosci.* **1**, 393-417. (DOI:10.1146/annurev-animal-031412-103647).

470 [55] Foo, S. A. & Byrne, M. 2017 Marine gametes in a changing ocean: Impacts of climate
471 change stressors on fecundity and the egg. *Mar Environ Res* **128**, 12-24.
472 (DOI:10.1016/j.marenvres.2017.02.004).
473 [56] Prasad, S., Tiwari, M., Pandey, A. N., Shrivastav, T. G. & Chaube, S. K. 2016 Impact of
474 stress on oocyte quality and reproductive outcome. *J Biomed Sci* **23**. (DOI:10.1186/s12929-
475 016-0253-4).
476 [57] Daxinger, L. & Whitelaw, E. 2012 Understanding transgenerational epigenetic
477 inheritance via the gametes in mammals. *Nat Rev Genet* **13**, 153-162.
478 (DOI:10.1038/nrg3188).
479 [58] Evans, J. P., Wilson, A. J., Pilastro, A. & Garcia-Gonzalez, F. 2019 Ejaculate-mediated
480 paternal effects: evidence, mechanisms and evolutionary implications. *Reproduction* **157**,
481 R109. (DOI:10.1530/rep-18-0524).
482 [59] Groothuis, T. G. G., Hsu, B. Y., Kumar, N. & Tschirren, B. 2019 Revisiting mechanisms
483 and functions of prenatal hormone-mediated maternal effects using avian species as a
484 model. *Phil Trans R Soc B* **374**. (DOI:10.1098/rstb.2018.0115).
485 [60] Perez, M. F. & Lehner, B. 2019 Intergenerational and transgenerational epigenetic
486 inheritance in animals. *Nat Cell Biol* **21**, 143-151. (DOI:10.1038/s41556-018-0242-9).
487 [61] Crean, A. J., Kopps, A. M. & Bonduriansky, R. 2014 Revisiting telegony: offspring inherit
488 an acquired characteristic of their mother's previous mate. *Ecol Lett.* **17**, 1545-1552.
489 (DOI:10.1111/ele.12373).
490 [62] Watkins, A. J., Dias, I., Tsuro, H., Allen, D., Emes, R. D., Moreton, J., Wilson, R., Ingram,
491 R. J. M. & Sinclair, K. D. 2018 Paternal diet programs offspring health through sperm- and
492 seminal plasma-specific pathways in mice. *Proc Natl Acad Sci U S A.* **115**, 10064-10069.
493 (DOI:10.1073/pnas.1806333115).
494 [63] Simmons, L. W. & Lovegrove, M. 2019 Nongenetic paternal effects via seminal fluid.
495 *Evol Lett* **3**, 403-411. (DOI:10.1002/evl3.124).
496 [64] Crean, A. J. & Bonduriansky, R. 2014 What is a paternal effect? *Trends Ecol Evol* **29**, 554-
497 559. (DOI:10.1016/j.tree.2014.07.009).
498 [65] Kekäläinen, J., Jokiniemi, A., Janhunen, M. & Huuskonen, H. 2020 Offspring phenotype
499 is shaped by the nonsperm fraction of semen. *J Evol Biol* **33**, 584-594.
500 (DOI:10.1111/jeb.13592).
501 [66] Parker, L. M., Ross, P. M. & O'Connor, W. A. 2009 The effect of ocean acidification and
502 temperature on the fertilization and embryonic development of the Sydney rock oyster
503 *Saccostrea glomerata* (Gould 1850). *Glob Chang Biol* **15**, 2123-2136. (DOI:10.1111/j.1365-
504 2486.2009.01895.x).
505 [67] Kekäläinen, J., Oskoei, P., Janhunen, M., Koskinen, H., Kortet, R. & Huuskonen, H. 2018
506 Sperm pre-fertilization thermal environment shapes offspring phenotype and performance.
507 *J Exp Biol* **221**, jeb181412. (DOI:10.1242/jeb.181412).
508 [68] Ritchie, H. & Marshall, D. J. 2013 Fertilisation is not a new beginning: sperm
509 environment affects offspring developmental success. *J Exp Biol* **216**, 3104-3109.
510 (DOI:10.1242/jeb.087221).
511 [69] Crean, A. J. & Marshall, D. J. 2009 Coping with environmental uncertainty: dynamic bet
512 hedging as a maternal effect. *Phil Trans R Soc B* **364**, 1087-1096.
513 (DOI:doi:10.1098/rstb.2008.0237).
514 [70] Mashoodh, R., Habrylo, I. B., Gudsnuk, K. M., Pelle, G. & Champagne, F. A. 2018
515 Maternal modulation of paternal effects on offspring development. *Proc R Soc B* **285**,
516 20180118. (DOI:doi:10.1098/rspb.2018.0118).

517   [71] Champagne, F. A. 2020 Interplay between paternal germline and maternal effects in
518   shaping development: The overlooked importance of behavioural ecology. *Funct Ecol* **34**,
519   401-413. (DOI:10.1111/1365-2435.13411).
520   [72] Kekäläinen, J. & Evans, J. P. 2018 Gamete-mediated mate choice: towards a more
521   inclusive view of sexual selection. *Proc R Soc B* **285**, 20180836.
522   (DOI:doi:10.1098/rspb.2018.0836).
523   [73] Smith, K. E., Byrne, M., Deaker, D., Hird, C. M., Nielson, C., Wilson-McNeal, A. & Lewis,
524   C. 2019 Sea urchin reproductive performance in a changing ocean: poor males improve
525   while good males worsen in response to ocean acidification. *Proc R Soc B* **286**, 20190785.
526   (DOI:10.1098/rspb.2019.0785).
527   [74] Crean, A. J., Dwyer, J. M. & Marshall, D. J. 2012 Fertilization is not a new beginning: the
528   relationship between sperm longevity and offspring performance. *PloS one* **7**, e49167.
529   (DOI:10.1371/journal.pone.0049167).
530   [75] Immler, S., Hotzy, C., Alavioon, G., Petersson, E. & Arnqvist, G. 2014 Sperm variation
531   within a single ejaculate affects offspring development in Atlantic salmon. *Biol Lett* **10**,
532   20131040. (DOI:10.1098/rsbl.2013.1040).
533   [76] Alavioon, G., Hotzy, C., Nakhro, K., Rudolf, S., Scofield, D. G., Zajitschek, S., Maklakov, A.
534   A. & Immler, S. 2017 Haploid selection within a single ejaculate increases offspring fitness.
535   *Proc Natl Acad Sci U S A.* **114**, 8053-8058. (DOI:10.1073/pnas.1705601114).
536   [77] Pitnick, S., Hosken, D. J. & Birkhead, T. R. 2009 Sperm morphological diversity. In *Sperm*
537   *biology: an evolutionary perspective* (eds. T. R. Birkhead, D. J. Hosken & S. Pitnick), pp. 69-
538   149. Oxford, Academic Press.
539   [78] Dowling, D. K., Nystrand, M. & Simmons, L. W. 2010 Maternal effects, but no good or
540   compatible genes for sperm competitiveness in Australian crickets. *Evolution* **64**, 1257-1266.
541   (DOI:10.1111/j.1558-5646.2009.00912.x).
542   [79] Simmons, L. W., Lovegrove, M. & Almbro, M. 2014 Female effects, but no intrinsic male
543   effects on paternity outcome in crickets. *J Evol Biol* **27**, 1644-1649. (DOI:10.1111/jeb.12418).
544   [80] Joseph, S. B. & Kirkpatrick, M. 2004 Haploid selection in animals. *Trends Ecol Evol* **19**,
545   592-597. (DOI:10.1016/j.tree.2004.08.004).
546   [81] Immler, S. & Otto, S. P. 2018 The evolutionary consequences of selection at the haploid
547   gametic stage. *Am Nat* **192**, 241-249. (DOI:10.1086/698483).
548   [82] Immler, S. 2019 Haploid selection in "diploid" organisms. *Annu Rev Ecol Evol S* **50**, 219-
549   236. (DOI:10.1146/annurev-ecolsys-110218-024709).
550   [83] Gur, Y. & Breitbart, H. 2006 Mammalian sperm translate nuclear-encoded proteins by
551   mitochondrial-type ribosomes. *Genes Dev.* **20**, 411-416. (DOI:10.1101/gad.367606).
552   [84] Bhutani, K., Stansifer, K., Ticau, S., Bojic, L., Villani, C., Slisz, J., Cremers, C., Roy, C.,
553   Donovan, J., Fiske, B., et al. 2019 Widespread haploid-biased gene expression in mammalian
554   spermatogenesis associated with frequent selective sweeps and evolutionary conflict.
555   *bioRxiv*, 846253. (DOI:10.1101/846253).
556   [85] Sharma, U. 2019 Paternal contributions to offspring health: role of sperm small RNAs in
557   intergenerational transmission of epigenetic information. *Front Cell Dev Biol.* **7**.
558   (DOI:10.3389/fcell.2019.00215).
559   [86] Jodar, M. 2019 Sperm and seminal plasma RNAs: what roles do they play beyond
560   fertilization? *Reproduction* **158**, R113. (DOI:10.1530/rep-18-0639).
561   [87] Champroux, A., Cocquet, J., Henry-Berger, J., Drevet, J. R. & Kocer, A. 2018 A decade of
562   exploring the mammalian sperm epigenome: paternal epigenetic and transgenerational
563   inheritance. *Front Cell Dev Biol.* **6**. (DOI:10.3389/fcell.2018.00050).

564 [88] Gapp, K., Jawaid, A., Sarkies, P., Bohacek, J., Pelczar, P., Prados, J., Farinelli, L., Miska, E.
565 & Mansuy, I. M. 2014 Implication of sperm RNAs in transgenerational inheritance of the
566 effects of early trauma in mice. *Nat Neurosci.* **17**, 667-669. (DOI:10.1038/nn.3695).
567 [89] Zhang, Y., Shi, J., Rassoulzadegan, M., Tuorto, F. & Chen, Q. 2019 Sperm RNA code
568 programmes the metabolic health of offspring. *Nat Rev Endocrinol* **15**, 489-498.
569 (DOI:10.1038/s41574-019-0226-2).
570 [90] Potok, M. E., Nix, D. A., Parnell, T. J. & Cairns, B. R. 2013 Reprogramming the maternal
571 zebrafish genome after fertilization to match the paternal methylation pattern. *Cell* **153**,
572 759-772. (DOI:https://doi.org/10.1016/j.cell.2013.04.030).
573 [91] Nelson, C. M. & Bunge, R. G. 1974 Semen analysis: evidence for changing parameters of
574 male fertility potential. *Fertil Steril.* **25**, 503-507. (DOI:10.1016/s0015-0282(16)40454-1).
575 [92] Levine, H., Jørgensen, N., Martino-Andrade, A., Mendiola, J., Weksler-Derri, D., Mindlis,
576 I., Pinotti, R. & Swan, S. H. 2017 Temporal trends in sperm count: a systematic review and
577 meta-regression analysis. *Hum Reprod Update.* **23**, 646-659.
578 (DOI:10.1093/humupd/dmx022).
579 [93] Mann, U., Shiff, B. & Patel, P. 2020 Reasons for worldwide decline in male fertility. *Curr*
580 *Opin Urol* **30**, 296-301. (DOI:10.1097/mou.0000000000000745).
581 [94] Rodprasert, W., Main, K. M., Toppari, J. & Virtanen, H. E. 2019 Associations between
582 male reproductive health and exposure to endocrine-disrupting chemicals. *Curr Opin Endocr*
583 *Metab Res* **7**, 49-61. (DOI:10.1016/j.coemr.2019.05.002).
584 [95] Tubbs, C. W. & McDonough, C. E. 2018 Reproductive impacts of endocrine-disrupting
585 chemicals on wildlife species: implications for conservation of endangered species. *Annu Rev*
586 *Anim Biosci.* **6**, 287-304. (DOI:10.1146/annurev-animal-030117-014547).
587 [96] Palmer, N. O., Bakos, H. W., Fullston, T. & Lane, M. 2012 Impact of obesity on male
588 fertility, sperm function and molecular composition. *Spermatogenesis* **2**, 253-263.
589 (DOI:10.4161/spmg.21362).
590 [97] McPherson, N. O. & Tremellen, K. 2020 Increased BMI 'alone' does not negatively
591 influence sperm function - a retrospective analysis of men attending fertility treatment with
592 corresponding liver function results. *Obes Res Clin Pract.* (DOI:10.1016/j.orcp.2020.03.003).
593 [98] Vrooman, L. A. & Bartolomei, M. S. 2017 Can assisted reproductive technologies cause
594 adult-onset disease? Evidence from human and mouse. *Reprod Toxicol.* **68**, 72-84.
595 (DOI:10.1016/j.reprotox.2016.07.015).
596 [99] Feuer, S. K. & Rinaudo, P. F. 2017 Physiological, metabolic and transcriptional postnatal
597 phenotypes of in vitro fertilization (IVF) in the mouse. *J Dev Orig Health Dis.* **8**, 403-410.
598 (DOI:10.1017/s204017441700023x).
599 [100] Guo, X. Y., Liu, X. M., Jin, L., Wang, T. T., Ullah, K., Sheng, J. Z. & Huang, H. F. 2017
600 Cardiovascular and metabolic profiles of offspring conceived by assisted reproductive
601 technologies: a systematic review and meta-analysis. *Fertil Steril.* **107**, 622-631.e625.
602 (DOI:10.1016/j.fertnstert.2016.12.007).
603 [101] Rexhaj, E., Paoloni-Giacobino, A., Rimoldi, S. F., Fuster, D. G., Anderegg, M., Somm, E.,
604 Bouillet, E., Allemann, Y., Sartori, C. & Scherrer, U. 2013 Mice generated by in vitro
605 fertilization exhibit vascular dysfunction and shortened life span. *J Clin Invest.* **123**, 5052-
606 5060. (DOI:10.1172/jci68943).
607 [102] Ramos-Ibeas, P., Heras, S., Gomez-Redondo, I., Planells, B., Fernandez-Gonzalez, R.,
608 Pericuesta, E., Laguna-Barraza, R., Perez-Cerezales, S. & Gutierrez-Adan, A. 2019 Embryo
609 responses to stress induced by assisted reproductive technologies. *Mol Reprod Dev.* **86**,
610 1292-1306. (DOI:10.1002/mrd.23119).

611 [103] Cooper, T. G., Noonan, E., von Eckardstein, S., Auger, J., Baker, H. W., Behre, H. M.,
612 Haugen, T. B., Kruger, T., Wang, C., Mbizvo, M. T., et al. 2010 World Health Organization
613 reference values for human semen characteristics. *Human reproduction update* **16**, 231-245.
614 (DOI:10.1093/humupd/dmp048).
615 [104] Pérez-Cerezales, S., Laguna-Barraza, R., de Castro, A. C., Sánchez-Calabuig, M. J., Cano-
616 Oliva, E., de Castro-Pita, F. J., Montoro-Buils, L., Pericuesta, E., Fernández-González, R. &
617 Gutiérrez-Adán, A. 2018 Sperm selection by thermotaxis improves ICSI outcome in mice. *Sci*
618 *Rep.* **8**, 2902. (DOI:10.1038/s41598-018-21335-8).
619 [105] Immler, S., Calhim, S. & Birkhead, T. R. 2008 Increased postcopulatory sexual selection
620 reduces the intramale variation in sperm design. *Evolution* **62**, 1538-1543.
621 (DOI:10.1111/j.1558-5646.2008.00393.x).
622 [106] Holt, W. V. & Van Look, K. J. W. 2004 Concepts in sperm heterogeneity, sperm
623 selection and sperm competition as biological foundations for laboratory tests of semen
624 quality. *Reproduction* **127**, 527-535. (DOI:10.1530/rep.1.00134).
625 [107] Waberski, D. 2018 Artificial insemination in domestic and wild animal species. In
626 *Animal Biotechnology 1: Reproductive Biotechnologies* (eds. H. Niemann & C. Wrenzycki),
627 pp. 37-64. Cham, Springer International Publishing.
628 [108] Garcia-Ruiz, A., Cole, J. B., VanRaden, P. M., Wiggans, G. R., Ruiz-Lopez, F. J. & Van
629 Tassell, C. P. 2016 Changes in genetic selection differentials and generation intervals in US
630 Holstein dairy cattle as a result of genomic selection. *Proc Natl Acad Sci U S A.* **113**, E3995-
631 4004. (DOI:10.1073/pnas.1519061113).
632 [109] Gardner, D. K. & Kelley, R. L. 2017 Impact of the IVF laboratory environment on human
633 preimplantation embryo phenotype. *J Dev Orig Health Dis.* **8**, 418-435.
634 (DOI:10.1017/s2040174417000368).
635 [110] Fraser, L., Strzezek, J. & Kordan, W. 2011 Effect of freezing on sperm nuclear DNA.
636 *Reprod Domest Anim.* **46 Suppl 2**, 14-17. (DOI:10.1111/j.1439-0531.2011.01815.x).
637 [111] Urbano, M., Dorado, J., Ortiz, I., Morrell, J. M., Demyda-Peyrás, S., Gálvez, M. J.,
638 Alcaraz, L., Ramírez, L. & Hidalgo, M. 2013 Effect of cryopreservation and single layer
639 centrifugation on canine sperm DNA fragmentation assessed by the sperm chromatin
640 dispersion test. *Anim Reprod Sci* **143**, 118-125. (DOI:10.1016/j.anireprosci.2013.10.005).
641 [112] Borini, A., Tarozzi, N., Bizzaro, D., Bonu, M. A., Fava, L., Flamigni, C. & Coticchio, G.
642 2006 Sperm DNA fragmentation: paternal effect on early post-implantation embryo
643 development in ART. *Hum Reprod* **21**, 2876-2881. (DOI:10.1093/humrep/del251).
644 [113] Alvarez Sedó, C., Bilinski, M., Lorenzi, D., Uriondo, H., Noblía, F., Longobucco, V., Lagar,
645 E. V. & Nodar, F. 2017 Effect of sperm DNA fragmentation on embryo development: clinical
646 and biological aspects. *JBRA Assist Reprod* **21**, 343-350. (DOI:10.5935/1518-0557.20170061).
647 [114] Pini, T., Leahy, T. & de Graaf, S. P. 2018 Sublethal sperm freezing damage:
648 Manifestations and solutions. *Theriogenology* **118**, 172-181.
649 (DOI:10.1016/j.theriogenology.2018.06.006).
650 [115] Nusbaumer, D., Da Cunha, L. M. & Wedekind, C. 2019 Sperm cryopreservation reduces
651 offspring growth. *Proc R Soc B* **286**. (DOI:10.1098/rspb.2019.1644).
652 [116] Chatterjee, A., Saha, D., Glasmacher, B. & Hofmann, N. 2016 Chilling without regrets:
653 deciphering the effects of cryopreservation on the epigenetic properties of frozen cells will
654 benefit the applications of cryo-technology. *EMBO reports* **17**, 292-295.
655 (DOI:10.15252/embr.201642069).
656 [117] Navarrete, F. A., Aguila, L., Martin-Hidalgo, D., Tourzani, D. A., Luque, G. M., Ardestani,
657 G., Garcia-Vazquez, F. A., Levin, L. R., Buck, J., Darszon, A., et al. 2019 Transient sperm

658   starvation improves the outcome of assisted reproductive technologies. *Front Cell Dev Biol.*

659   **7**, 262. (DOI:10.3389/fcell.2019.00262).

660   [118] Navarrete, F. A., Alvau, A., Lee, H. C., Levin, L. R., Buck, J., Leon, P. M., Santi, C. M.,

661   Krapf, D., Mager, J., Fissore, R. A., et al. 2016 Transient exposure to calcium ionophore

662   enables in vitro fertilization in sterile mouse models. *Sci Rep.* **6**, 33589.

663   (DOI:10.1038/srep33589).

664   [119] Manier, M. K., Belote, J. M., Berben, K. S., Novikov, D., Stuart, W. T. & Pitnick, S. 2010

665   Resolving mechanisms of competitive fertilization success in *Drosophila melanogaster*.

666   *Science (New York, N.Y.)* **328**, 354-357. (DOI:10.1126/science.1187096).

667   [120] Wylde, Z., Crean, A. & Bonduriansky, R. 2020 Effects of condition and sperm

668   competition risk on sperm allocation and storage in neriid flies. *Behavioral Ecology* **31**, 202-

669   212. (DOI:10.1093/beheco/arz178).

670   [121] Rickard, J. P., Pool, K. R., Druart, X. & de Graaf, S. P. 2019 The fate of spermatozoa in

671   the female reproductive tract: A comparative review. *Theriogenology* **137**, 104-112.

672   (DOI:10.1016/j.theriogenology.2019.05.044).

673