REPRODUCTION
REVIEW

# Reproductive science and the future of the planet

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## Abstract

**Reproductive sciences have made major contributions to human health, livestock production and environmental management in the past and will continue to do so in future. In collaboration with other disciplines, reproductive scientists can provide scientifically valid information that will allow the rational development of policies on topics such as declining fertility in men and women, livestock breeding efficiencies, climate change, pest animal control, wildlife management and environmental influences. It is imperative that the reproductive sciences are recognised by the community and policy makers as important contributors to future health and welfare of animals, humans and the planet if these potential benefits are to be captured and utilised. Reproductive Health Australia (RHA) was launched recently to advocate for reproductive biology as a national health, economic and social priority. This short review provides a snapshot of why it is imperative that reproductive science receives the recognition that is due to it and provides examples of how it can contribute to the future of the planet.**

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## Introduction

Reproductive technologies have been used by humankind for centuries. These relate mainly to farming practices such as placing stones in camel uteri to control breeding and castrating ruminants and chickens to enhance growth. These technologies were developed through trial and error and not by any empirical experimentation. It was not until the Renaissance Period and later that there are reports of empirical experimentation to identify the reproductive organs of animals and how they function. Of note are Leonardo di Vinci's famous drawings of copulation, the experiments of Harvey on red deer and the explosion of scientific knowledge after the invention of the microscope eventually leading to the identification of eggs and spermatozoa (Cobb 2006).

What is notable about these early experimentalists is that the individuals were polymaths who had interests well beyond the reproductive sciences. And so it is today that individuals and groups working in the field of reproductive science come from many different disciplines, and more often than not do not call themselves reproductive scientists. This practice is becoming even more common as collaboration to address complex problems expands to other disciplines well outside what could be defined as reproductive science.

As a result, the extent and significance of the discipline of reproductive science is not appreciated publically in the same way as, for example, oncology, mental health and immunology. Reproductive health is an essential component of overall health of all animals because life would not exist without reproduction. Furthermore, fertility status is an indicator or predictor of future overall health (Cedars *et al.* 2017) particularly for non-communicable diseases in adulthood.

There are other factors that mitigate against an appreciation of the importance and contributions of the reproductive sciences to the health and welfare of the planet. In the field of human fertility, the successes of assisted reproductive technologies (ARTs) have captured the imagination of the public to the detriment of other important human reproductive health issues, for example, contraceptive use or preterm birth and developmental origins of human diseases. Another factor is the tension between the use of growth stimulants in cattle and the effects that these (commonly steroid) agents may have on wildlife, human health and the environment. The eradication of pest animals like rabbits by a process called 'gene drive' has concerned environmentalists because of the risk that it could adversely impact wildlife and domesticated species including both pets and agriculturally important animals (Moro *et al.* 2018). There is a dramatic rate of extinction of many animal species, particularly in Australia, with consequences for biological diversity. There is a significant role for the reproductive sciences to save many of these species from extinction by employing


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existing and future reproductive technologies. Finally, an under-appreciation of reproductive sciences also arises due to cultural and religious sensitivities and stigmas associated with reproductive health and reproductive rights. Demographic studies report that 12–15% of couples are unable to conceive 1 year after having unprotected sex, and after 2 years, 10% of couples remain infertile (<www.nichd.nih.gov/health/topics/infertility/common>). The inability of women to have a child or to become pregnant can result in being ostracised, feared or shunned; furthermore, it may be used as grounds for divorce and justify a denial to access family traditions (https://www.who.int/reproductivehealth/topics/infertility/keyissues/en/). These attitudes make it difficult to investigate the causes and incidence of infertility and provide or devise and implement appropriate treatments.

Nevertheless, research in the reproductive sciences has identified the underlying causes of many problems and led to many improvements in our reproductive health, in breeding domesticated animals and in the conservation and management of wildlife. These achievements get overshadowed by a focus on ART in humans as the one issue of importance to the public.

## Examples of the contributions by reproductive sciences

Some examples of the contributions by reproductive sciences to human health, livestock production and conservation management are described in Boxes 1, 2 and 3. The collaborative nature of these achievements deserves emphasis, as well as the social and economic benefits. Many of the technologies, such as artificial insemination (AI), *in vitro* fertilisation (IVF), *in vitro*

### Box 1: Decreasing human sperm counts and testicular dysgenesis syndrome (TDS)

One example of an area ripe for reproductive research is the declining sperm count in men. A recent systematic review and meta-regression analysis (Levine *et al.* 2017) has confirmed a significant temporal decline (50–60%) in sperm concentrations (SC) and total sperm counts in men from Western countries between 1981 and 2013. These men were not selected for fertility and there was no evidence of the decline slowing down in recent years. These data have serious implications for future male fertility and underline the urgent need for research to identify the causes of this decline.

The declining trend in SC has implications for fertility because an increasing number of men will have SC at or below the threshold of 40 million/mL associated with a decline in the probability of conception (Bonde *et al.* 1998). Furthermore, low sperm counts have been associated with overall morbidity and mortality (Levine *et al.* 2017).

Skakkebaek *et al.* (2001) have proposed that declining SCs are a component of testicular dysgenesis syndrome (TDS) that includes a rising incidence of testicular cancer, declining semen quality (that includes SC), a rising incidence of undescended testes and hypospadias, and as a consequence, a growing demand for assisted reproduction, particularly the use of intra-cytoplasmic sperm injection (ICSI). TDS is associated with a decline in serum testosterone concentrations in healthy men and an increasing incidence of testicular germ cell cancer, particularly in young men. Given the rates of change in these parameters over a short period, it seems more likely that they are the result of environmental influences rather than genetic differences, although the latter cannot be dismissed. Small polymorphic differences in essential but susceptible genes could change gene sensitivity to environmental and lifestyle factors.

There is a large body of literature showing that male animals exposed either *in utero* or perinatally to environmental or natural oestrogens (e.g. DDT), androgens or phthalates can develop hypospadias, undescended testes, low sperm counts, intersex conditions, teratomas or tumours (Skakkebaek *et al.* 2001). It is plausible to assume that these compounds will have similar effects in human males although empirical data are not available yet.

Skakkebaek (2017) proposed the following research questions: 'What is the role of exposure to endocrine disrupting chemicals in reproductive trends? What is the role of lifestyle factors, including recreational drugs? (Is) dysgenesis of the fetal testes caused by maternal exposure? Why is the incidence of testicular cancer increasing among young men of reproductive age?' To properly address these questions will require research efforts by not just reproductive scientists but also collaboration with scientists, clinicians and health authorities in other fields that recognise the urgent need for this research.

It is clear that technologies such as AI, IVF and IVM to alleviate infertility have enormous personal and social benefits for individuals. However, research on reproduction in humans involves more than infertility. There is now abundant evidence that early origins of disease, particularly non-communicable diseases like diabetes, high blood pressure and cardiovascular disease, can be traced back to events that influence the quality of spermatozoa, eggs and a pregnancy. Furthermore, recent research shows that metabolic syndrome in pregnant women increases their risk for pregnancy complications including preeclampsia and gestational diabetes by 2–4 times (Grieger *et al.* 2018).

**Box 2: The role of reproductive technologies in livestock reproduction**

Assisted reproduction programmes in the dairy industry originally focused on detection of oestrus and the timing of insemination to optimise pregnancy (Stevenson & Britt 2017). More recent approaches use breeding programmes to optimise the decisions about breeding, but the goal remains minimisation of the interval from calving to first AI resulting in successful pregnancy. Four factors determine reproductive efficiency in dairy herds: the voluntary waiting period, the insemination rate, pregnancy per AI and pregnancy loss (Thomasen *et al.* 2016). These are constantly monitored to optimise reproductive efficiency. Initially, use of timed AI for first AI followed by detection of oestrus with resynchronisation of cows that are not pregnant followed by a second round of insemination is the most profitable breeding strategy.

Attempts to improve reproductive outcomes through embryo technologies are only worthwhile commercially if any resultant increase in pregnancy rate is larger than that obtainable by AI. This is currently not the case, although constant improvements in the technology or changes in management systems may alter this conclusion in the future (Heikkila & Peippo 2012). Of course, in breeding operations aimed at producing genetically elite animals, the cost equations are different and embryo technologies are more widely used. Particularly attractive to the average producer would be the ability to sex any embryo prior to transfer either through the use of sexed semen and IVF or molecular screening and selection of embryos (Wheeler *et al.* 2006, Ettema *et al.* 2017). This is likely to be one of the first widespread uses of embryo technology in the dairy industry.

In the beef industry the situation is different in a number of ways (e.g. the sex of the offspring generally is less important as both steers and cows are used for meat), and it is made more complex by the very different management systems used in intensive and extensive beef production systems. In intensive management systems where animals are held in enclosures and so can be readily monitored on an ongoing basis and where either bulls are excluded until required for breeding or timed AI is employed to induce pregnancy, the goals and methodologies are not vastly different from those in the dairy industry. Transfer of embryos produced either *in vitro* (i.e. IVP embryos) or embryos derived *in vivo* (i.e. IVD embryos) usually after superovulation and insemination again does not have broad utilisation although in stud breeding operations to produce high genetic quality bulls and increasingly high-quality cows the situation is different. Commercial embryo transfer operations started in the 1970s and worldwide hundreds if not thousands of businesses exist in many countries (Dahlen *et al.* 2014). The driver here is the genetic quality of the animal produced. When high-quality embryos are transferred with or without cryopreservation, high rates of pregnancy are achievable if suitably prepared recipients are available and animals are managed appropriately. Poor results are not always the result of failure of the technology. Extraneous factors such as disease outbreaks or the vagaries of the volatile changes in cattle and meat or milk prices etc play their own roles. However, the quality of the embryos produced for transfer is vital, but failure of recipient selection and management is often also a contributing factor limiting success. Gains can be made by improving all steps in the pipeline from embryo generation, to transfer, to pregnancy management. This is not to suggest that improvements in technology will not alter the picture. Improvements in cryopreservation of IVD embryos such as those which have undergone biopsy for genetic assessment and the issue of abnormal pregnancies with some IVD embryos, especially cloned embryos, need to be resolved if related to abnormal epigenetics (Urrego *et al.* 2014). However, the advent of rapid genetic assessment of embryos ideally so that transfer could occur within a MOET (multiple ovulation and embryo transfer) cycle will occur within the near future. This will provide new options for the embryo transfer industry and will alter the economics of embryo transfer making transfer a more attractive financial option.

In extensive breeding situations such as is found in South America, in particular Brazil, and in the northern parts of Australia, herd management and control of breeding is very different because animals cannot be monitored readily except at the annual or biannual roundups when selection of animals for marketing and identification of which new heifers enter the breeding programme occurs. In 2015 (IETS Newsletter) the global transfer rates for IVP embryos was 77% of that for IVD embryos and no doubt as more recent figures become available the gap will have narrowed further. Nearly three quarters of IVP embryo usage occurs in Brazil. This is attributable to peculiarities of the management systems such as poor superstimulation in *Bos indicus* breeds which dominate in South America, the expense of FSH required in MOET programmes and the low cost of labour all favour use of IVP. Interestingly, in northern Australia where *Bos indicus* breeds or *Bos indicus* × *Bos Taurus* cross bred animals also predominate but where labour costs and other production costs are considerably higher, IVP transfer numbers are much lower. No doubt other factors such as producer interest and acceptance also play a part.

In conclusion, the promise of IVP will need to be accompanied by further improvements in embryo culture systems, in cryopreservation/vitrification technologies, in identification of markers to readily select the highest quality embryos and crucially, methodologies to permit rapid and accurate genetic profiling of IVP embryos, will be major drivers to increase use of IVP embryos. When these are accompanied by more specialist applications such as the use of sexed semen in dairy cows or collection of oocytes from prepubertal animals, the possibilities for the cattle industry encompassed in the use of IVP embryos are substantial.

A specific example of the application of reproductive technologies in the livestock industry is the Repronomics programme focussing on fertility improvement in cattle in Northern Australia (https://www.beefcentral.com/genetics/repronomics-fertility-project-update-at-mundubbera-beefup-forum/). Low reproductive rates in northern Australian beef herds are a significant factor limiting productivity. This collaborative, five-year Repronomics project, now in its third year, aims to improve the evaluation of beef herds for a number of economically important performance traits, in particular female fertility.

In the fat lamb industry in Australia, it has been estimated that a 10% increase in conception rate results in a 6.2% increase in the gross margin/hectare, while a 10% increase in the lamb survival rate results in a 12.1% increase in the gross margin, based on $A 72/hectare baseline gross margin (https://publications.mla.com.au). This demonstrates very clearly the importance for profitability of improving livestock fertility through reproductive science.

**Box 3: Saving the kakapo**

Successful reproduction in wildlife has important ecological and evolutionary consequences, with repercussions for the viability of populations, the survival of species and the function and sustainability of entire ecosystems.

The International Union for Conservation of Nature (IUCN) estimates that 25% of mammals, 12% of birds, 20% of reptiles, 30% of amphibians, 20% of fishes, 30% of invertebrates and 55% of plant species are threatened with extinction. Extinction of species occurs because of human activities that are modifying the environment (e.g. climate change, habitat fragmentation), as well as overhunting, fishing and poaching (Comizzoli 2015). Placing a quantitative (economic) benefit on wildlife research is difficult. A primary aim of animal conservation is to understand and sustain biodiversity; the loss of even a single species can compromise the entire ecosystem. Reproductive research on wildlife benefits from advances in research in the human infertility and oncofertility and livestock production fields, despite the different objectives of these programmes (e.g. overcoming infertility in humans, more efficient/higher quality food production in livestock, and retention of genetic diversity in wildlife). Nonetheless, all share a common goal in 'ensuring reproductive health and preserving fertility (Comizzoli *et al.* 2010). The use of AI in wildlife species has been of noted success, as shown, for example in the giant panda (*Ailuropoda melanoleuca*), black-footed ferret (*Mustela nigripes*) and scimitar oryx (*Oryx dammah*). Embryo-related technologies, by contrast, have not been applied to any great degree principally because of the paucity of data on cross-species embryology (Comizzoli *et al.* 2010).

Within species, reproduction can affect population health through its influence on key demographic parameters, including the quality and quantity of offspring that are produced (Candolin & Wong 2012, Wong & Candolin 2015). At the ecosystem level, because different species are linked to each other through complex interactions, changes in reproduction that alters the population demography of one species can have knock-on effects that cascade well beyond the initial disturbance to impact the ecological community as a whole (Palkovacs & Dalton 2012). From an applied perspective, insights from reproductive biology can be critical to conservation and management (Cook & Sgro 2018). For instance, reproductive science can provide knowledge relevant to managing and controlling invasive species as seen, for example, in the development of non-surgical sterilisation methods to control feral animal populations (Hall *et al.* 2017). An understanding of reproductive biology can also be important in managing and conserving species that are at risk of extinction, such as the application of assisted reproductive technologies in conservation breeding programmes (Byrne & Silla 2010, Comizzoli *et al.* easily be overlooked – but are otherwise critical – in the success of wildlife conservation efforts. An example of this is seen in the kakapo.

The kakapo (*Strigops habroptilus*) is a ground-dwelling, nocturnal parrot endemic to New Zealand (Fig. 1). Once common, populations of this now critically endangered bird have been decimated following the introduction of feral predators into New Zealand. Not surprisingly, considerable effort has been devoted to saving the species from extinction, including the supplementary feeding of wild birds – a widely used tool in the management of threatened wildlife. Work carried out by Clout *et al.* (2002), however, uncovered that supplementary feeding of kakapo had unintended consequences by causing a male-biased offspring sex ratio. Drawing on sex allocation theory (Trivers & Willard 1973), the researchers showed that maternal condition affected offspring sex ratio in this species, resulting in well-fed females producing more sons than daughters. As recruitment of females was critical to an already male-biased adult population, changes were made to supplementary feeding regimes that allowed kakapo conservators to control maternal condition and, in so doing, manipulate the sex ratio of chicks to maximise the chances of species recovery (Robertson *et al.* 2006). Such studies underscore how integration of reproductive science, in this case, an understanding of sex allocation theory from evolutionary biology, can lead to better management and conservation outcomes for wildlife.

**Figure 1** The kakapo (*Strigops habroptilus*) is a ground-dwelling, nocturnal parrot endemic to New Zealand. Kakapo.photo. Chris Burmingham.

maturation of oocytes (IVM) and embryo transfer (ET), developed in one species have been applied to other species with remarkable success.

## Raising the public profile of the reproductive sciences

Greater public awareness of the importance of the reproductive sciences is needed. The reproductive sciences want recognition and financial support for its capacity to make essential contributions to the health, welfare and economic well-being of the people and animals on our planet. Our scientific discipline is robust, very productive and has made profound contributions to human health, livestock production and environmental sustainability and will continue to do so in the future. It is not our role to take political positions on issues of the day. We reproductive scientists want to emphasise our individual and collaborative capacities to investigate, in a robust scientific way, the issues and problems facing our planet and to provide evidence-based information that forms the bases of rational and valuable policies.

## Reproductive Health Australia

An organisation called Reproductive Health Australia or RHA was launched recently. RHA is an alliance of reproductive scientists whose members come from all fields of research in reproductive health from human fertility and domestic animal production to wildlife conservation and environmental management.

RHA will advocate for reproductive biology as a national health, economic and social priority. It is independent of government and will inform and educate the public, government and the scientific sector on critical issues in reproduction that impact on a sustainable Australia and the enormous benefits of translating the discoveries and advances in research in reproductive health. It will promote the capacity and strengths in reproductive health research, particularly the cross disciplinary potential of reproductive health research. It will also engage reproductive health researchers across all career stages and foster a mentoring system that ensures ongoing support of our early and midcareer researchers. RHA has a public website, also to be available on social media, featuring news of recent reproductive research and its application, and a quarterly newsletter for members, who will be able to contact each other through the website. Individual membership is open and free. Other RHA activities include approaches to Federal politicians and sponsoring seminars and public lectures. It is planned to extend membership to notable public figures who may support the vision and mission of RHA.

To summarise, the focus of RHA lies in advocating and publicising the health, economic and social benefits of reproductive health research, and the capacity of reproductive health research to investigate the important issues and to translate the findings into beneficial outcomes.

More information is provided on our website. www.reproductivehealthaustralia.org.au

## Conclusions

Reproductive scientists across all disciplines can provide scientifically based information for the rational development of policies on topics such as declining fertility in men and women, livestock breeding efficiencies, climate change, pest animal control, wildlife management and environmental influences. It is imperative that the reproductive sciences are recognised at the community and policy level as important contributors to our future health and welfare.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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