The cost of living longer

Fertility trades with immunity and life expectancy

Philip Hunter

Sexual reproduction and the mixing of alleles that it entails boosts diversity, but also poses a dilemma for individual organisms. Given that each organism has ultimately limited resources for reproduction, maintenance and immunity, the choice between fertility and long-term survival is one between two opposite poles of selection that operate across many animal and plant species. The balance between fertility and immunity has direct implications for human health; indeed a growing body of work is investigating the links between disease and reproductive biology. Moreover, epidemiological data shows that humans, especially in developed countries and particularly women, are becoming less fertile, but more immune to infectious and other diseases. This, in addition to factors such as improved healthcare, is further increasing human lifespan in wealthy societies.

The hypothesis that investing more energy and resources into maintenance and immunity comes at the expense of fertility was first proposed by Thomas Kirkwood (1977), now Director of the Institute for Ageing and Health at Newcastle University in the UK. His theory was supported by epidemiological and historical data (Westendorp & Kirkwood, 1998), as well as animal experiments and molecular evidence. Yet, the exact nature of the link between reproduction and immunity has remained elusive.

One problem, at least for plant and animal species that have internal fertilization, is the cost of this reproductive strategy whereby gametes from one partner, usually the male, enter the other. This is the heart of the sexual immunity problem, according to Michael Siva-Jothy, an entomologist at Sheffield University in the UK, whose interest in this relationship between reproduction and immunity has led him to study

the phenomenon in vertebrates. "I would say, when you go from external to internal fertilisation, you create a huge problem," he said. "It's the same problem probably across all taxa, in that recipients of gametes are faced with how to defend their internal environment from non self, while allowing sperm to get through. Sperm are non self even to males, so must be in females."

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Moreover, the link between reproduction and immunity extends beyond the female genital tract to include pregnancy in mammals and male fertility. A joint study between Princeton University in the USA and Edinburgh University in the UK found that among a population of isolated sheep in the Outer Hebrides— islands off the coast of Scotland—both males and females with high levels of antibodies were able to survive the occasional harsh winters that occur there, but reproduced less than did sheep with lower levels of antibodies during less harsh winters (Graham *et al.*, 2010). During intervening periods, often lasting several years, the number of individuals with lower levels of antibodies within the population would increase, before being reduced again when the next harsh winter arrived.

The fact that both male and female sheep were affected rules out anything to do with the female genital tract. "We do not know why the autoantibody responses were associated with reduced annual breeding success," commented Andrea Graham, lead author of the study from Princeton University. "The same pattern occurred in both males and females, which suggests a resource allocation 'trade-off'."

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According to David Schneider, whose laboratory at Stanford University in the USA specializes in innate immunity and host–parasite interactions in *Drosophila*, the resource theory—that a living organism has limited resources available for growth, maintenance and reproduction—plays a major role in the relationship between fertility and immunity. "There seems to be some sort of limit on how much a body can do," he said. "We can't just keep doing more and there is a reason that we don't have our immune response on all of the time."

By its nature, the resource theory is hard to establish beyond all doubt, but there is growing evidence that resource allocation plays an important role in a third instance in humans and probably all mammals: an internal conflict between mother and fetus. This too involves a trade-off, but for a different reason, because the interests of the fetus and the mother do not exactly coincide. The fetus, half of whose genes are paternal, wants to obtain as much of the mother's resources as possible to optimize its growth during pregnancy. The mother's best interest, however, lies in distributing her available resources equally among all the fetuses she will conceive during her lifetime. This conflict is played out through the immune systems of father, fetus and mother, and in particular through the major histocompatibility class (MHC) molecules. During pregnancy, the mother exhibits an inflammatory response to the paternal MHC proteins expressed by the fetus, which is often cited as evidence for the maternal–fetal conflict theory.

A successful pregnancy therefore requires that the mother's body tolerates the presence of MHCs and other antigens of paternal origin that are expressed by the fetus. There is some evidence that the father can manipulate this response: if the paternal MHC proteins are very different to the maternal ones, this tends to stimulate growth of the placenta, thereby increasing the resources available to the fetus (Madeja *et al*, 2011).

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The conflict theory has implications for the health of both fetus and mother, since the inflammatory response can cause significant harm or even death to both. It can, for example, cause an excessive immunological response to low virulence bacteria such as *Fusobacteria* that are commonly present in the upper genital tract and normally cause few problems. This excessive immune response is associated with premature delivery (Gomez *et al*, 1997). There is also evidence that pre-eclampsia—a systemic maternal disease that is characterized by

hypertension and proteinuria, and which is potentially fatal to both mother and fetus—is caused in some cases by maternal–fetal conflict (Ness, 2004).

According to David van Bodegom from the Department of Gerontology and Geriatrics at Leiden University in the Netherlands, the strength of the mother's immunity can determine whether conception will occur in the first place. He referred to a study finding that women attending IVF clinics because of problems conceiving children were much more likely to suffer spontaneous abortions and at the same time had elevated immune function.

Van Bodegom suggested that such findings have significant societal implications, given the negative selection pressure against fertility in women caused by the trend to have smaller families. "In the past, the next generation would be produced by a limited number of very fertile women who had large families, while now all women have 1.8 to 2.4 children depending on the country," he said. Less fertile mothers receive assistance through IVF and other measures to conceive, while more fertile ones use contraceptive drugs and other methods to limit their reproduction. "So now only a few children are descendants of very fertile women," said van Bodegom.

There is a parallel trend in wealthier nations towards having children later in

life. "The Netherlands has the European record for the highest average age of [mothers giving birth to their] first child, I think now 30 years," said van Bodegom. The first trend suggests that fertility problems among women will increase, as will the need for assistance. The second trend towards having children later would select for women who retain their fertility for longer.

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The two trends—lower fertility overall but retaining it for longer—seem to pull in opposite directions but might actually favour the same women. According to van Bodegom, women with late menopause tend to live longer, which might suggest they have stronger immune systems and in turn perhaps lower overall fertility. This is still speculation at present, but there is a clear correlation between the late onset of menopause and longevity (Ossewaarde *et al*, 2005). Selection pressure for delayed menopause onset should therefore lead to increased life expectancy among women, van Bodegom suggested.

But there is a downside to late motherhood: the high physiological demands of pregnancy itself. A recent study in the UK found that although overall levels of death during pregnancy or childbirth had decreased dramatically since surveys began in 1952, the maternal death rate from indirect causes had actually increased over the last 20 years (Cantwell *et al*, 2011). These indirect causes include cardiac disease, hypertension, diabetes and neurological disorders brought on or accentuated by pregnancy.

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The report prompted David Williams, a Consultant Obstetric Physician at University College Hospital in London, and others to argue in the *British Medical Journal* that this rise in death rate was the result of an increase in average age of pregnant mothers (Nelson-Piercy *et al*, 2011). Older women tend to weigh more, which increases the risk of diabetes and hypertension in particular during pregnancy, Williams argued. Older women were also less well equipped to deal with the physical and physiological rigours of pregnancy, and this in turn translated into increased risk of disease and complications. Given that this trend towards later pregnancies is unlikely to be reversed, Williams and his colleagues have called for more specialist physicians and greater awareness among all doctors.

Although the greatest focus on the links between fertility, immunity and longevity has been on women, there is mounting evidence that the story includes men. Some studies demonstrate a link between immunity and spermatogenesis in humans, mostly showing that sperm itself is recognized as non-self in men and can trigger the production of anti-sperm antibodies (ASAs). This would explain why there is a barrier between the testes, where sperm are produced and stored, and the blood: to prevent sperm antigens from leaking out and triggering ASA production.

Yet, the barrier is not impenetrable: chronic infection of the genitals can cause the production of ASAs, perhaps by maintaining a high level of immunity. Moreover, exposure to heavy metals can also trigger the production of antibodies acting against sperm and cause male infertility, which would partly explain an overall decline in male fertility observed during the past half century or more in some countries, possibly triggered by exposure to mercury in dental tooth fillings (Podzimek *et al*, 2005).

However, despite the presence of ASAs from the man, sperm are still able to reach the oocyte. Even so, some researchers have suggested that by binding to the sperm, ASAs make it unable to complete the so-called acrosome reaction needed to penetrate the oocyte (Bohring *et al*, 2004). This reaction occurs in some form in almost all sexually reproducing species after the fusion between sperm and oocyte, and enables the acrosome—a cap-like structure on the head of the sperm—to release its contents. These contents include surface antigens and enzymes that break down the coat of the oocyte and allow fertilization to occur. Antibodies attached to the sperm head can prevent the all-important acrosome reaction from taking place.

Immunity therefore seems linked to fertility in both men and women, although it remains to be seen whether the inverse relationship applies in men: that is, individuals who are more fertile also have lower levels of immunity. However, the fate of sheep in the Outer Hebrides suggests this might well be the case. In fact, another epidemiological study of human longevity and reproductive success indicates that there is such a trade-off in both men and women (Thomas *et al*, 2000).

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the cost of fertility. It is also clear that this development is not over yet and that it will have profound health and social implications for both sexes in future generations.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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