

Research round-up

Highlights from reproductive-health studies. By Claire Ainsworth

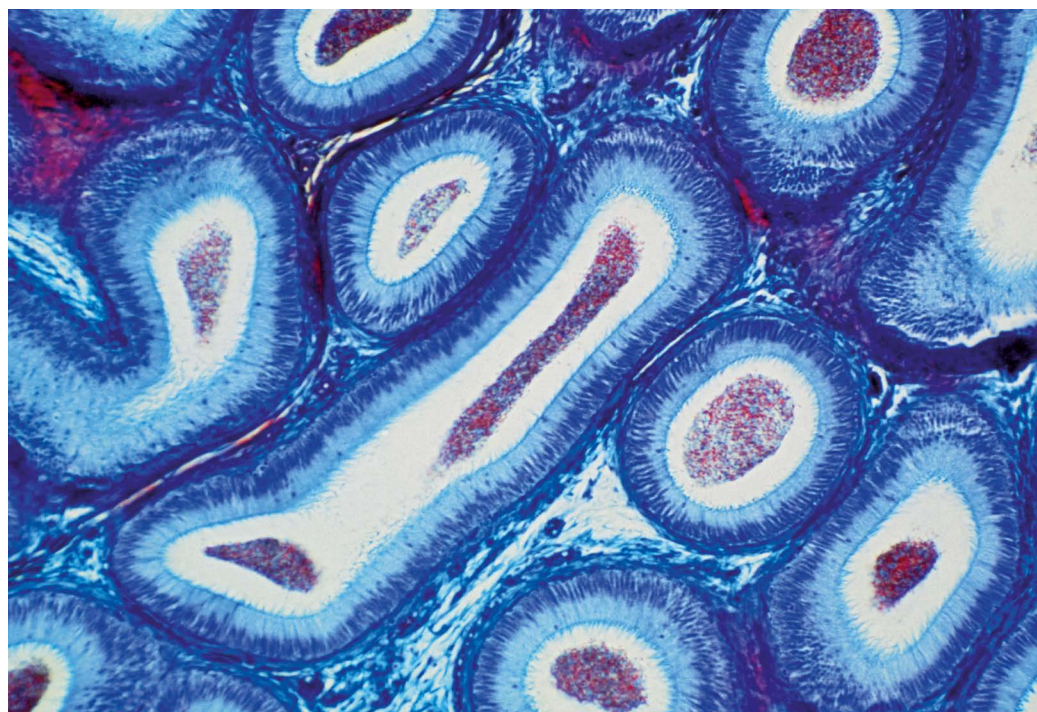
Controlling whether sperm are fertile

A hitherto mysterious communication system between two parts of the male reproductive system has had one of its messengers unmasked. The finding opens new avenues in the study of infertility and could aid the development of non-hormonal contraceptives.

Sperm travel from germ cells in the testes to a long, winding tube called the epididymis, where they develop the ability to swim and fertilize eggs. Researchers have suspected that signals flowing from the testis enable the epididymis to develop correctly so it can nurture sperm. Problems with this process are thought to contribute to infertility.

Researchers had previously found that a receptor called ROS1 is needed for the epididymis to develop properly, but no one had identified any signals to it from the testis.

A team of researchers led by Martin Matzuk at Baylor College of Medicine in Houston, Texas, and Masahito Ikawa at Osaka University in Japan has now found a signal: a protein called NELL2 that is secreted by germ cells in the testis. When the team knocked out NELL2 function in mice, the males produced immotile sperm and were infertile. The team showed that the lack of NELL2 hampered the development of the epididymis. Restoring



Light micrograph of the epididymis, where sperm mature (sperm are stained red, inside the white lumen).

NELL2 function in the germ cells was found to restore male fertility.

Science **368**, 1132–1135 (2020)

Contraceptives that target meiosis

The mechanisms that govern the final steps of cell division in a human egg, which are essential for fertilization to succeed, are promising targets for new, non-hormonal contraceptives.

A team of researchers led by Carol Hanna at Oregon Health & Science University in Portland has developed a framework for identifying and testing drugs that might block the mechanism, potentially making the process faster and cheaper. They have also identified two promising candidates.

The team focused on an enzyme called WEE2 kinase

that controls the final steps of meiosis (the division of sex cells). Women lacking functional WEE2 kinase are infertile, so blocking the production or action of the enzyme could have a contraceptive effect.

Because the molecule is active only in developing eggs and sperm, drugs that target it are unlikely to have side effects in other tissues. Such drugs, which are non-hormonal and would not affect the timing of menstrual periods, could be used routinely or as emergency contraception. Current emergency contraception targets the hormones that trigger ovulation, but because fertilization takes place later, a drug that targets WEE2 kinase could increase the time available for contraception.

The team identified possible drug binding sites on WEE2 kinase, aided by computer modelling, and screened

26,000 compounds. The researchers tested the ability of potential drugs to stop WEE2 kinase activating its target molecule, called CDK1. They then tested the drugs' ability to block meiosis in cow eggs *in vitro*. Finally, they tested for effects on the division of non-sex cells. This helped the team to identify two promising leads for further evaluation.

Biol. Reprod. **103**, 368–377 (2020)

Cash incentives boost the use of IUDs

Offering cash incentives to doctors to provide information to women about long-acting reversible contraceptives (LARCs), such as intra-uterine devices (IUDs), led to greater use of such contraceptives, according to a study of British medical records. The tactic was

also followed by a fall in the number of abortions.

Devices such as IUDs, which are placed in the uterus and can release either hormones or copper, can effectively prevent pregnancy for several years. Other LARCs include hormone injections, which last for up to 3 months, and hormonal implants placed under the skin of the arm, which work for 3 years. They are extremely effective, thanks in part to their 'set-and-forget' nature, but their uptake is low, even in high-income countries.

In 2009, the British government introduced a pay-for-performance scheme for doctors to encourage the use of LARCs. Doctors were asked to provide information about LARCs to more than 90% of girls and women aged 13–54 attending a clinic for contraceptive care. Doctors were paid for giving the information, not for issuing LARC prescriptions.

A team led by Richard Ma at Imperial College London used a statistical approach known as an interrupted time series to study the medical records of almost 3.3 million women in Britain before and after the target was introduced. They found that four years after the scheme began, LARC prescriptions were 13% higher, and the number of abortions was 38% lower, than would have been predicted. The impact was greatest in women aged 20–24 and those from poorer backgrounds.

PLoS Med. **17**, e1003333 (2020)

Unmet need for birth control calculated

About 270 million women around the world do not have sufficient access to effective contraception, according to the first study to assess the needs of all women of reproductive age. The research offers more-comprehensive estimates of this and other family-planning

indicators than previous studies based only on married and cohabiting women have done.

One of the goals of the United Nations 2030 Agenda for Sustainable Development is universal access to family planning. The ability to track global progress towards such goals requires robust collection and analysis of data on contraceptive use in women of reproductive age. Until recently, however, estimates of contraceptive use have been based only on married women, or women cohabiting with their partners, and not on single or non-cohabiting women.

To address this gap, a team led by UN demographer Vladimíra Kantorová, based in New York City, compiled data on contraceptive use and need in all women of reproductive age, from multiple sources, including surveys from 195 countries. The researchers then applied Bayesian modelling, which had previously been used only on family-planning data from married women, to data on their single peers.

Among their findings, the researchers showed that unmarried women represent an increasing proportion of contraceptive users worldwide, but that in 43 countries, of which 32 were classified as low-income, less than half of women's need for modern contraception is being met. In many low-income countries, the population of women of reproductive age is set to increase dramatically between now and 2030. The implication, say the authors, is that it will be difficult to expand family-planning services quickly enough to meet their needs.

PLoS Med. **17**, e1003026 (2020)

Endometrium study could aid fertility

Researchers have charted gene activity at the single-cell level in the lining of the human

womb, the endometrium, throughout the menstrual cycle. The endometrium undergoes a monthly cycle of remodelling, shedding and regeneration, with a brief period when an embryo can be implanted, known as the window of implantation. Charting the molecular and cellular processes in the endometrium will aid the understanding of female fertility and offer insights for regenerative medicine.

Some previous studies have looked at how the cell types in the endometrium contribute to its function, but none has studied gene activity at the level of individual cells across the menstrual cycle.

A team led by Carlos Simon and Stephen Quake at Stanford University in California has now done just that. The team obtained biopsies at various points in the menstrual cycle from 19 women undergoing egg donation, and studied gene expression in individual cells using the RNA-seq technique.

The researchers studied the behaviour of seven cell types, including one that has never previously been characterized. They found four major phases of endometrial change. A dramatic shift in gene activity associated with the window of implantation could be used to identify it to aid fertility treatments.

Nature Med. **26**, 1644–1653 (2020)

Unexpected pattern in abortion statistics

The rate of unintended pregnancies has declined globally since the mid-1990s, but the proportion that end in abortion has increased, according to a new statistical analysis. Women in low- and middle-income countries experience the highest rates of unplanned pregnancies, and abortion rates are generally higher in countries that legally restrict access to it.

Estimates of unintended pregnancy and abortion rates provide essential information about trends in sexual and reproductive health and autonomy that are needed to inform investment in health programmes and policies. However, the available data vary in quality and reliability from country to country.

To tackle this problem, a team led by Jonathan Bearak at the Guttmacher Institute in New York compiled data on pregnancy intentions and abortions from national surveys, official statistics and literature searches. The researchers then applied a form of Bayesian statistical modelling to estimate the rates of unintended pregnancy and abortion.

The researchers found that in 2015–19, the global annual unintended pregnancy rate was 64 per 1,000 women aged 15–49, down from 79 per 1,000 women in 1990–94. In 2015–19, women in low-income countries had the highest rates of unintended pregnancy, at 93 per 1,000, compared with 34 per 1,000 in high-income countries.

The global abortion rate, however, was similar in 1990–94 and 2015–19, indicating that the proportion of unintended pregnancies being terminated had increased.

The team found no evidence that abortion rates were lower in countries where access is legally restricted. This finding, the authors say, points to a need for more research into how women access abortion in these settings, as well as into the safety and health consequences of unsafe abortion on health and well-being.

Lancet Glob. Health **8**, e1152–e1161 (2020)



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