Meiosis and fertility: an old wives’ tale

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For a variety of different reasons, women are delaying attempts to get pregnant until later in their lives. However, age-related decline in egg quality is a major factor in otherwise-unexplained infertility. What are the underlying biochemical processes contributing to this loss of fertility?

Current trends on childbearing in the UK

Women in Western nations are in control of their own lives, as never before. Career opportunities and financial independence are making real progress towards gender equality. Alongside this, a revolution has taken place in fertility choices. Many women plan pregnancies around their jobs, education, housing and lifestyle priorities. Life partners may be selected at a later age, and changes of partner are more frequent.

The Office for National Statistics regularly publishes data about the ages of women giving birth. Their most recent edition shows the expected trends; more women aged 40+, 35–39 and 30–34 are having babies than in earlier years, while fewer teenagers and 20-somethings are having children (Figure 1). A radio commentator, that I happened to hear discussing the latest dataset, thought this was good as children born would have more secure homes and more experienced parents. But he did not mention the hidden costs of this revolution, because biology is now at odds with society. Many women planning for a child in their later reproductive years will need assistance to become pregnant, while many others will spend a lot of time, money and energy trying unsuccessfully to have a baby.

The problems of trying to be an older mum

Around 1 in 7 UK couples will experience difficulty in conceiving when they start trying to do so. The later they start trying, the lower their fertility is likely to be, purely as a result of being older. Reproductive ageing is particularly abrupt in women, with fertility declining from around 30 years of age, the decline accelerates steeply at 37 years, reaching very low levels in the mid-40s. Figure 2 shows the live birth rates after IVF treatment in the UK, highlighting the association between a woman’s age and the chances of success, when using her own eggs.

As well as having lower chances of becoming pregnant, older women are faced with increasing chances of conceiving a pregnancy that carries chromosomal errors. These errors underlie an increasing risk of miscarriage, termination due to diagnosed abnormality, and birth of an affected child. In particular, trisomy 21 (Down syndrome) is the commonest chromosomal disorder, causing mental and physical problems in children and a lower life expectancy. Most of the chromosomal errors causing reduced fertility and increased risk of chromosomally affected conceptions arise during the process of egg formation.

How eggs form

Meiosis is the highly specialized cell division that produces haploid eggs or sperm from a diploid stem
cell. Eggs have a peculiar history, being formed and entering meiosis in the ovaries of a female foetus before birth. This means that the egg that will become a grandchild is already present in the ovary of a female foetus – the future mother – while it is being carried by the pregnant woman – who is the egg’s future grandmother. A woman’s environment during pregnancy therefore has potential to affect not just her daughter but her grandchild too.

Large numbers of eggs enter meiosis before birth, but the number present declines continually from birth until the menopause, at which time the supply of eggs reaches critically low numbers. Fertility in adult life depends upon the surviving population, known as the ovarian reserve, remaining arrested in the meiotic cell cycle for many years. During a woman’s reproductive lifespan, some eggs become active, growing for several months in an immature state, and just before ovulation they finally become mature and ready to meet a sperm. It is this preovulatory maturation process, comprising the first meiotic division, that is particularly error-prone. Although it has been known for decades that the risks of certain chromosomal abnormalities increase with maternal age, the underlying mechanisms controlling chromosome movements and ageing in eggs have only recently become possible to study in detail.

**Our research**

In my work, I speak with patients in advance of their IVF treatment, requesting research consents. I may also see patients afterwards, particularly if their treatment has been unsuccessful and they are seeking reasons for the lack of success and a prognosis for future treatment outcomes. I study eggs and embryos during clinical treatment using non-invasive time-lapse imaging, aiming to link how they look under the microscope, and the times at which key events take place, with the potential for normal or abnormal development. In this way, I try to understand the underlying biology, but without disturbing the egg or embryo as it grows. However, for more detailed analysis, I collaborate with basic researchers to study chromosome movements directly, using technology not available in an IVF clinic. My key collaborators are Professor Andrew McAinsh (University of Warwick), Professor Adele Marston (University of Edinburgh) and Professor Eva Hoffmann (University of Copenhagen).

Our research aims to understand the basic mechanisms underpinning chromosome segregation in meiosis, which also relates to understanding the causes of increasing chromosomal abnormalities in children of older mothers.

**Figure 2.** The chances of a live birth according to female age, in couples using their own eggs and sperm to attempt pregnancy by IVF. These UK national data are presented in ‘Fertility treatment 2014-2016: trends and figures’. Published in March 2018 (www.hfea.gov.uk/media/2544/hfea-fertility-treatment-2014-2016-trends-and-figures.pdf). Note the steep decline in live birth rates with female age. The difference between the lines is because some patients, particular older women, may have up to three embryos transferred simultaneously.

**Figure 3.** Comparison of chromosome and kinetochore arrangements in mitosis and the first division of meiosis. In mitosis, chromatids are always pulled to separate poles of the spindle. In the first division of meiosis, the sister chromatids move together towards the same pole, so kinetochores have a side-by-side arrangement. Reproduced from Patel J et al Biology Open 2015 Dec 30;5(2):178-84, with permission from the publisher. [http://bio.biologists.org/content/5/2/178.long]

**Older eggs come unstuck**

While there are several hypotheses, one of the most popular is that molecules holding the meiotic chromosomes together deteriorate as time goes by, thus allowing chromosomes to drift apart, predisposing to difficulties when segregation of chromosomes is required just before ovulation. It is believed that these cohesive molecules are laid down before birth as the eggs enter meiosis, however, they are not replenished. So by the time the egg is preparing to ovulate, the chromosome structure has been
waiting in an arrested state for many years. Inevitably, the older the woman, the longer the chromosomes have been in this arrested state. The first meiotic division, that occurs a few hours before ovulation, is complex and error-prone. This division started in the foetus, when homologous pairs of replicated chromosomes came together, synapsed and underwent genetic recombination, resulting in four intertwined chromatids with crossing over points. For these to be separated into haploid sets of chromosomes, such as are present in eggs or sperm, two divisions (meiosis 1 and meiosis 2) are required which each halve the number of chromosomes present. Therefore, in meiosis 1, two chromatids have to arrive at the same spindle pole, so some of the connecting proteins between them have to remain strong, whereas others have to dissolve to allow progression to anaphase 1. Protein clusters (known as kinetochores) which attach the chromosomes to the tubules comprising the spindle, control the orientation of the chromosome attachments. These kinetochores are critical to ensuring that chromosomes are pulled in the right direction at meiosis 1. In this way, meiosis is distinctly different to mitosis, where chromosomes must separate from their partners, as shown in Figure 3.

**Highlighting the problem**

Our work uses molecular markers to highlight key parts of the kinetochores and the chromosomes, and then applies high power microscopy to identify and reconstruct the detailed structure and relative orientations of the component parts. This reveals the organization of the kinetochores (Figure 4), and helps to identify where errors with chromosomal movements may have occurred.

For this research, we study eggs that are not appropriate for use in IVF treatment, either because they are immature, or because they didn’t fertilise when first inseminated with sperm. We fix and stain them using antibodies, or we highlight chromosomes in live cells and follow them using high power time-lapse microscopy. We then challenge the eggs to continue maturing, or to fertilize, and observe the movements of chromosomes in real time using live cell imaging. Many of these divisions show errors, allowing us to study the mechanisms by which abnormalities arise.

In eggs from older women having IVF treatment, we have found that the kinetochores are further apart in their pairs at metaphase of meiosis 1 than is the case in younger women (Figure 5). Moreover, kinetochores in humans appear different in structure from those in other animal species, notably mice where most study has been undertaken. Kinetochores in humans are distinctly separate, while those in mice and other species may be fused together, which would presumably help to hold them in place during the prolonged meiotic arrest since before birth, possibly explaining some of the differences between animals and humans in terms of the incidence of chromosomal anomalies in embryos.
The increasing distance between kinetochore pairs with maternal age suggests that the chromosomes to which they are attached are moving apart with time.

**So what can we do about it?**

There is nothing with current technology that can be done to avoid or correct errors in meiosis 1. Older women whose own eggs are unable to generate a pregnancy can receive donated eggs from a younger woman, but any resulting baby is therefore genetically unrelated to themselves. It is also an expensive, emotionally challenging and arduous option, so its avoidance by having children at a younger age, or perhaps by banking eggs when young for personal use in future, may be worth considering. Young and aspiring professional women need access to this information to help inform their decisions when planning their future families.

In the fertility centre, some women have a clinical problem which may affect egg quality, but many do not have a defined cause of infertility, and often age is the main contributing factor to their inability to become pregnant. One reason for writing this article is to highlight the difficulty that some older women may experience when attempting pregnancy. I would like to encourage any woman who wishes to have children, to balance the timing of that decision against other important aspects of her life, in full knowledge of the facts around fertility and reproductive ageing.

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