
This is an excerpt from my Ph.D. thesis introduction chapter. This section was dedicated to my family and friends and was meant to be understood by a general audience with only basic notions of biology.

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1. It all starts with a cell

For millennia, scientists believed that life could arise spontaneously from non-living matter. Robert Hooke first described plant cells in 1665, but it was almost two centuries after this discovery that we finally arrived at the consensus that all living things are either a cell or composed of cells and that *all* cells come from pre-existing ones. Today we know that every one of us began as one single cell: the zygote. The zygote is the fertilized egg from which an endless diversity of cells can develop, shaping the human body. The biggest one of these cells is the oocyte itself, the main object of study of this thesis.

In sexual reproduction, the fusion of two gametes forms the zygote, which will become a new individual. This process is called fertilization, and it allows the genetic information from the two gametes to combine. To avoid doubling the number of chromosomes upon fertilization, sexual reproduction requires the DNA content to be halved through a special cell division called meiosis.

During meiosis, a diploid cell (with a complete set of chromosomes) divides twice, becoming haploid (with only half the number of chromosomes). These two cell divisions are called meiosis I and meiosis II, and they happen sequentially after a single DNA replication event. Two haploid gametes can then fuse to restore the chromosome number during fertilization.

Prior to meiotic divisions, homologous chromosomes pair up and recombine, exchanging genetic material. These recombination events are characteristic of meiosis and an essential source of genetic shuffling and variation; they are a motor for evolution.

1.1. Microscopic mistakes with big consequences

Errors in chromosome segregation during cell division can result in aneuploidy, i.e., an incorrect number of chromosomes in a cell. Aneuploidy in somatic cells is often associated with tumor development. In germ cells (sperm and oocytes), it most often leads to pregnancy loss. Aneuploid gametes can still be fertilized, originating an aneuploid embryo. However, during embryonic development, most aneuploidies become lethal. Aneuploid embryos that give rise to live births inevitably carry developmental disorders caused by the abnormal chromosome number. Aneuploidy is the most frequently identified cause of involuntary pregnancy loss (Hassold and Hunt 2001). Genetic analysis of miscarried embryos indicates

that most (50-76%) miscarriages during the first trimester occur due to aneuploidy (Lathi et al. 2007).

Spontaneous miscarriage occurs in 15-20% of all pregnancies (Blohm, Fridén, and Milsom 2008), and the risk of pregnancy loss increases with maternal age (Nagaoka, Hassold, and Hunt 2012). After the age of 45 years, about three out of four pregnancies result in fetal loss (Andersen et al. 2000). These rates may be an underestimation because embryonic development is likely often interrupted before a pregnancy is even detected. Together, these problems contribute to couples' infertility, which affect 17-30% of couples in France (Slama et al. 2012).

Only a small set of chromosomes allows an extra pair (trisomy, three copies), and only chromosome X is tolerant for a single copy (monosomy). Embryos presenting trisomies of chromosomes 13, 18, and 21 can be viable. In cases where a live birth occurs, the trisomy perturbs normal development and leads to multiple malformations corresponding to Patau's, Edwards, and Down's syndromes, respectively. Sex chromosome aneuploidies are more permissive if there is at least one X chromosome. Individuals may live with a variety of X and Y imbalance combinations. Well-described cases include Turner syndrome (X0), Klinefelter syndrome (XXY), and Jacobs syndrome (XYY).

1.2. An oocyte's hard life

Oocytes are some of the cells with the longest lifespans in the human body. They are among the select group of cells that accompany us from before birth without regeneration. Sperm, on the other hand, are continuously produced throughout adulthood. This means that each egg fertilized to produce a new baby had been in the mother's ovaries since she was just a fetus herself.

Meiosis itself takes place at an entirely different rhythm in oocytes and sperm. In adult males, new germ cells are regularly recruited to start meiosis. They undergo the two meiotic divisions and specialize by gaining a tail and losing most of their cytoplasm. They are ready to move out and try to find an oocyte to pair up with. In contrast, oocytes all enter meiosis at the same time in the fetal ovary, and they arrest in the early stages of meiosis (Prophase I, after having replicated their DNA and recombined homologous chromosomes). Starting at puberty, individual oocytes are stimulated to grow, and, in humans, one (sometimes two) fully grown

oocyte is ovulated each month. At this point, after years in Prophase I, the oocyte resumes meiosis, but it arrests again, this time in Metaphase II. Astonishingly, oocytes only truly finish meiosis if a sperm cell fertilizes them.

Size is another parameter for which sperm and oocytes are polar opposites. Gametes are both the largest and the tiniest cells in the human body: while the oocyte takes first place as the biggest human cell, the sperm runs last, as the smallest (**Figure 1.1**).

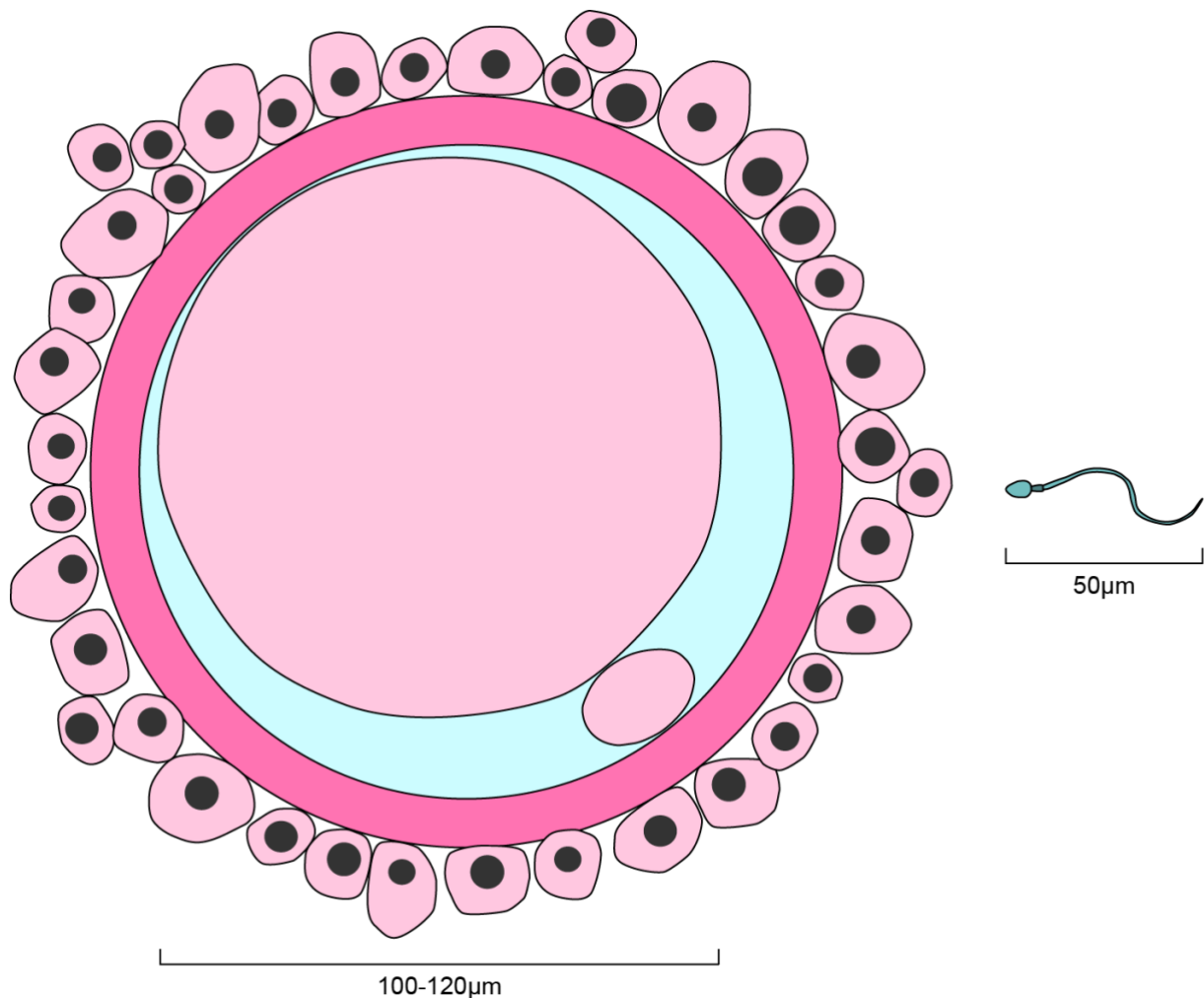


Figure 1.1 Illustration of the size difference between a human oocyte and a sperm cell

The represented oocyte is ready for fertilization, having extruded its first polar body. The *zona pellucida* (in bright pink) and granulosa cells surround the oocyte.

Their huge cytoplasm, stop-start cell cycle, and long lifespans are among the characteristics that make oocytes such a challenging environment in which to separate chromosomes. They partly explain the high rate of mistakes these cells make during the meiotic divisions. Indeed, female meiosis is a very error-prone cell division. Chromosome segregation errors occur more

frequently in oocytes than in sperm or the average somatic cell. Between 30 and 70% of human oocytes are aneuploid, compared to only 1-4% of sperm cells (Nagaoka, Hassold, and Hunt 2012). This prevalence increases with age and affects couples' fertility. Most errors are thought to occur during the first meiotic division, which, as we will see, is a very particular cell division.

Studying meiosis and its frequent errors leading to aneuploidy is crucial to understand why mistakes happen and explain infertility and recurrent pregnancy loss. These conditions and the assisted reproduction cycles proposed to circumvent them are emotionally draining, particularly when the cause is left unidentified. I hope that a deeper understanding of the meiotic divisions will contribute to better understand, destigmatize, and ultimately improve the treatment of involuntary childlessness.