**Lecture - Fertilization**

From Embryology

*Embryology - 18 Aug 2015* 

**Introduction**

This lecture and the associated laboratory will cover male and female gametogenesis and fertilisation.

Development is 1 embryonic cell producing about $10^{13}$ (100,000,000,000,000) cells in the adult at any one time (over time with cell death and ongoing replacement this is substantially more).

This is where the first embryonic cell begins! Fertilization is the fusion of haploid gametes, egg (oocyte) and sperm (spermatozoa), to form the diploid zygote. Note though there can be subtle differences in the fertilization process which occurs naturally within the body or through reproductive technologies outside the body, the overall product in both cases is a diploid zygote.

**Some Recent Research** - Meiosis Podcast Biosights 18 March 2013 - Breaking egg symmetry (http://jcb.rupress.org/content/200/5/567/suppl/DC2) | JCB 16 June 16 2014

How sperm get into the zona (http://jcb.rupress.org/content/205/6/754.2.full)

Lecture - Print PDF


**Lecture Objectives**

1. Broad understanding of reproductive cycles.
2. Understand the key features of gametogenesis.
3. Understand the differences in male and female gametogenesis.
4. Brief understanding of the differences between mitosis and meiosis.
5. Understanding of the events in fertilization.

**Lecture Resources**

- Cell division - 3 types
- Historic drawing of human oocyte and spermatozoa
Human Reproductive Cycle

Sexual reproduction in most species is regulated by regular endocrine changes, or cycles, in the female. These cycles begin postnatally, function for variable times and can then decrease or cease entirely.

- Human reproduction is regulated in females by the **menstrual cycle**, a regular cyclic hormonal change which coordinate changes in the ovary and internal reproductive tract. This cycle commences at puberty and ends at menopause.
- Non-primates (rats, mice, horses, pig) reproduction is regulated in females by the **estrous cycle** (British spelling, oestrous).

### Female
- Menstrual Cycle a regular cycle of reproduction (28 days)
- begins at puberty, release of 1 egg (oocyte) every cycle
- Endocrine controlled (HPG axis) **Hypothalamus - Pituitary - Gonad**

### Male
- continuous production of sperm (spermatozoa)
- begins at puberty, release millions of spermatozoa
- Endocrine controlled (HPG axis) **Hypothalamus - Pituitary - Gonad**

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**References**


**Cell Division Links:** Meiosis | Mitosis | Lecture - Cell Division and Fertilization | Spermatozoa Development | Oocyte Development | Fertilization | Zygote

- Menstrual Cycle | Oocyte | Zona pellucida | Spermatozoa | Meiosis | Fertilization | Mitosis | Week 1


The following chapter links only work with a UNSW connection.

- First Week of Human Development (http://www.unsw.eblib.com.wwproxy0.library.unsw.edu.au/patron/Read.aspx?p=1430154&pg=63)
- Second Week of Human Development (http://www.unsw.eblib.com.wwproxy0.library.unsw.edu.au/patron/Read.aspx?p=1430154&pg=63)


The following chapter links only work with a UNSW connection.

Gametogenesis

Meiosis in the gonad (ovary or testis) produces the haploid gametes, oocyte and spermatozoa (egg and sperm). Meiosis time course and final gamete number differs between female and male.

Male - Spermatogenesis

Human spermatozoa (electron microscope)

Mouse spermatozoa (electron microscope)
The testes have two functions.

1. produce the male gametes or **spermatozoa**
2. produce male sexual hormone, **testosterone** (internal and external genitalia, sex characteristics)

- **Spermatogonia** - are the diploid first cells of spermatogenesis
- **Primary spermatocytes** - large, enter the prophase of the first meiotic division
- **Secondary spermatocytes** - small, complete the second meiotic division
- **Spermatid** - immature spermatozoa
- **Spermatozoa** - differentiated gamete

**Spermatozoa development:**
- primordial germ cell - spermatogonia
- primary spermatocyte - secondary spermatocytes - spermatid

**Sertoli cells** (support cells)

**Interstitial cells** or Leydig cells (produce hormone)

**Female - Oogenesis**

The ovaries have two functions.

1. produce the female gametes or **oocytes**
2. produce female hormones, estrogen and progesterone (secondary sex characteristics, menstrual cycle)
In an adult human female the development of a primordial follicle containing an oocyte to a preovulatory follicle takes in excess of 120 days.

**Human Ovary Follicle Development**

In a human ovary, follicle development involves the following stages:

- **Ovarian Follicle Stages:** primordial follicle - primary follicle - secondary follicle - tertiary follicle - preovulatory follicle

**Follicle cells** (support cells) **Theca cells** (produce hormone)

### Meiosis Differences

**Male Meiosis**
- Meiosis initiated continuously in a mitotically dividing stem cell population
- 4 gametes produced / meiosis
- Meiosis completed in days or weeks
- Meiosis and differentiation proceed continuously without cell cycle arrest
- Differentiation of gamete occurs while haploid after meiosis ends
- Sex chromosomes excluded from recombination and transcription during first meiotic prophase

MBoC - Figure 20-27. The stages of spermatogenesis

**Female Meiosis**
- Meiosis initiated once in a finite population of cells
- 1 gamete produced / meiosis
- Completion of meiosis delayed for months or years
Female gametogenesis

Early zygote showing polar bodies

The Cell - Figure 14.37. Meiosis of vertebrate oocytes (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=cooper.figgrp.2492)

**Polar Bodies**

- In female gametogenesis only a single (1) haploid egg is produced from meiosis. In male gametogenesis four (4) haploid sperm are produced from meiosis. So what happens to all the extra DNA in producing this single egg?
  - In Meiosis 1 the "extra" DNA is excluded to the periphery as a 1st polar body, which encloses the extra DNA.
  - In Meiosis 2 the "extra" DNA is once again excluded as a 2nd polar body. The first polar body may also under go meiosis 2 producing a 3rd polar body.
- These polar bodies are not gametes.
- Polar bodies appear to have no other function other than to dispose of the extra DNA in oogenesis.
  - Recent research in mice suggest that the position of oocyte polar body may influence fertilization site.

**Meiosis Polar Body Movie**

**Fertilization**

Gamete formation, menstrual cycle and fertilisation will also be covered in detail in this week's Laboratory. Fertilization is the complete process resulting in the fusion of haploid gametes, egg and sperm, to form the diploid zygote. The recent development of aided fertilization is described as in vitro fertilization (in vitro = "in glass", outside the body, IVF). Clinically, all these aided fertilization techniques are grouped as Assisted Reproductive Technologies or ART.

- Oogenesis - 1 gamete produced/meiosis + 3 polar bodies, meiosis is slow, 1 egg produced and released at ovulation
- Spermatogenesis - 4 gametes produced/meiosis, meiosis is fast, 200-600 million sperm released at ejaculation

**Fertilization Movies**

**Fertilization Site**

- Fertilization resulting in embryo development usually occurs in first 1/3 of uterine tube (oviduct, Fallopian tube)
- The majority of fertilized oocytes do not go on to form an embryo
- Fertilization can also occur outside uterine tube associated with Assisted Reproductive Technologies (IVF, GIFT, ZIFT...) and ectopic pregnancy
- Oocyte ovulation - release from the ovary with associated cells, into peritoneal cavity, uterine tube fimbria then into uterine tube (oviduct, uterine horn, fallopian tube) and epithelial cilia mediated movement.
- Spermatozoa ejaculation - deposited in vagina, movement of tail to "swim" in uterine secretions through cervix, uterine body and into uterine tube, have approximately 24-48h to fertilize oocyte.

Prior to the fertilization process commencing both the gametes complete of a number of biological processes.

- **Oocyte Meiosis** - completes Meiosis 1 and commences Meiosis 2 (arrests at Metaphase II).
- **Spermatoza Capacitation** - following release (ejaculation) and mixing with other glandular secretions, activates motility and acrosome preparation.
- **Migration** - both oocyte and spermatozoa.


**Gamete Movement Movies**
Ejaculation
- about 3.5 ml, containing 200 - 600 million spermatozoa
- by volume less than 10% spermatozoa
- accessory glands contribute majority of volume (60% seminal vesicle, 10% bulbourethral, 30% prostate)

Male Infertility
- Oligospermia (Low Sperm Count) - less than 20 million sperm after 72 hour abstinence from sex
- Azoospermia (Absent Sperm) - blockage of duct network
- Immotile Cilia Syndrome - lack of sperm motility

Capacitation
- spermatozoa activation process - removal of glycoprotein coat and seminal proteins and alteration of sperm mitochondria

Spermatozoa motility
- tail of spermatozoa provide movement by microtubules
- energy for this movement is provided by mitochondria in tail initial segment

Chemotaxis
- oocyte cumulus cells release progesterone (may also be other oocyte and follicular fluid factors)

Acrosome Reaction
- exocytosis of acrosome contents (calcium mediated) MBoc - Figure 20-31. The acrosome reaction that occurs when a mammalian sperm fertilizes an egg (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mboc4.figgrp.3741)
- enzymes to digest the zona pellucida
- exposes sperm surface proteins to bind ZP2

Membrane fusion
- between spermatozoa and oocyte cell membranes, allows sperm nuclei passage into egg cytoplasm
- membrane fusion also initiates oocyte processes to block polyspermy

Fertilization - Oocyte

Oocyte: Membrane depolarization - Cortical reaction - Meiosis 2 completion

Membrane Depolarization
- caused by spermatozoa membrane fusion, acts as primary block to polyspermy (fertilisation by more than one spermatozoa)

Cortical Reaction
- Inositol triphosphate (IP3) pathway elevates intracellular calcium, exocytosis of cortical granules
- enzyme alters ZP2 so it will no longer bind sperm plasma membrane
- MBoc - Figure 20-32. How the cortical reaction in a mouse egg is thought to prevent additional sperm from entering the egg (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mboc4.figgrp.3743)

Meiosis 2
- completion of 2nd meiotic division
- forms second polar body (third polar body may be formed by meiotic division of the first polar body)
Formation of the Zygote

Early Zygotes

- Pronuclei - Male and Female haploid nuclei approach each other and nuclear membranes break down
- Chromosomal pairing, DNA replicates, first mitotic division
- Sperm contributes - centriole which organizes mitotic spindle
- Oocyte contributes - mitochondria (maternally inherited)

Sex Determination

- Based upon whether an X or Y carrying sperm has fertilized the egg, should be 1.0 sex ratio.
- Actually 1.05, 105 males for every 100 females, some studies show more males 2+ days after ovulation.
- Cell totipotent (equivalent to a stem cell, can form any tissue of the body)

Men - Y Chromosome

- Y Chromosome carries Sry gene, protein product activates pathway for male gonad (covered in genital development)

Women - X Chromosome

- Gene dosage, one X chromosome in each female embryo cell has to be inactivated
- Process is apparently random and therefore 50% of cells have father's X, 50% have mother's X
- Note that because men only have 1 X chromosome, if abnormal, this leads to X-linked diseases more common in male that female where bothe X's need to be abnormal.

Abnormalities

- The most common chromosome abnormality is aneuploidy, the gain or loss of whole chromosomes.
- Caused by meiotic nondisjunction, the failure of chromosomes to correctly separate homologues during meiosis I or sister chromatids during meiosis II.
- Down Syndrome - caused by an extra copy of chromosome 21. Abnormal Development - Trisomy 21 (Down Syndrome) Maternal Age

- Chromosomal translocations occur when there is an inappropriate exchange of chromosomal material. Philadelphia chromosome (http://visualsonline.cancer.gov/retrieve.cfm?imageid=7153&dpi=72&fileformat=jpg)
- Philadelphia chromosome - piece of Chr9 exchanged with Chr22 Generates truncated abl, overstimulates cell production, leads to chronic myelogenous leukemia
Hydatidiform Mole

- **Complete Mole** - Only paternal chromosomes.
- **Partial Mole** - 3 sets of chromosomes (triploidy) instead of the usual 2.

**Next**

- Lab 1 - Gametogenesis and Fertilisation

**Homework**

Beginning your online work - Working Online in this course

1. Make your own page.
   1. **Log-in** to the embryology website using your student ID and Zpass.
   2. Click your **student number** (shown in red at the top right of the screen following log-in)
   3. **Create** page using the tab at the top of the page, and save.
2. How would you identify your Type in a group and add to your page.
3. What was the most interesting thing you learnt in today's lecture?

If you have done the above correctly your ZID should be blue and not red on this page ANAT2341 2015 Students.

**UNSW Embryology Links**

- Spermatozoa Development
- Oocyte Development
- Fertilization
- Trisomy 21 (Down Syndrome)

**Cell Division Links:** Meiosis | Mitosis | Lecture - Cell Division and Fertilization | Spermatozoa Development | Oocyte Development | Fertilization | Zygote

**References**

**Online Textbooks**


- **Molecular Biology of the Cell** 4th ed. Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter

- **Molecular Cell Biology** by Lodish, Harvey; Berk, Arnold; Zipursky, S. Lawrence; Matsudaira, Paul; Baltimore, David; Darnell, James

- **The Cell**

  - **A Molecular Approach**


  - **IV. Cell Regulation**

  - **Chapter 14. The Cell Cycle**

  - **The Eukaryotic Cell Cycle**

  - **Overview of the Cell Cycle and Its Control**

  - **Figure 13-2. Current model for regulation of the eukaryotic cell cycle**

  - **Movies Proposed alternative mechanisms for chromosome congression.**

  - **Centromeric attachment of microtubules.**

  - **The stages of mitosis and cytokinesis in an animal cell.**

- **Search**

  - **Bookshelf**

  - **cell division**

  - **mitosis**

  - **meiosis**

  - **fertilization**

  - **Pubmed**

  - **cell division**

  - **mitosis**

  - **meiosis**

  - **fertilization**

- **Reviews**

  - **Dennis W Stacey, Masahiro Hitomi**

  - **Cell cycle studies based upon quantitative image analysis.**

  - **Cytometry A:** 2008, 73(4):270-8

  - **[PubMed:18163464]**

  - **Christoph Schorl, John M Sedivy**

  - **Analysis of cell cycle phases and progression in cultured mammalian cells.**

  - **Methods:** 2007, 41(2):143-50

  - **[PubMed:17189856]**

- **Terms**

  - **asthenozoospermia**

  - **-(asthenospermia) Term for reduced sperm motility and can be the cause of male infertility.**

  - **blood-testis barrier**

  - **-(BTB) Formed by tight junctions, basal ectoplasmic specializations, desmosome-like junctions and gap junctions between adjacent Sertoli cells near the basement membrane of the seminiferous epithelium.**

  - **diploid**

  - **-(Greek,**

  - **di = double + ploion = vessel) Having two sets of chromosomes, the normal state for all cells other than the gametes.**

  - **haploid**

  - **-(Greek,**

  - **haploos = single) Having a single set of chromosomes as in mature germ/sex cells (oocyte, spermatooza) following reductive cell division by meiosis. Normally cells are diploid, containing 2 sets of chromosomes.**

  - **Leydig cell**

  - **-(interstitial cell) Male gonad (testis) cell which secrete the androgen testosterone, beginning in the fetus. These cells are named after Franz von Leydig (1821 - 1908) a German scientist who histologically described these cells.**

  - **meiosis**

  - **-(The cell division that occurs only in production of germ cells where there is a reduction in the number of chromosomes (diploid to haploid) which is the basis of sexual reproduction. All other non-germ cells in the body divide by mitosis.**

  - **mitosis**

  - **-(The normal division of all cells, except germ cells, where chromosome number is maintained (diploid). In germ cell division (oocyte, spermatooza) meiosis is a modified form of this division resulting in reduction in genetic content (haploid). Mitosis, division of the nucleus, is followed by cytokinesis the division of the cell cytoplasm and the cytoplasmic contents. cytokinesis overlaps with telophase.**

  - **sperm annulus**

  - **-(Jensen's ring; Latin,**

  - **annulus = ring) A region of the mammalian sperm flagellum connecting the midpiece and the principal piece. The annulus is a septin-based structure formed from SEPT1, 4, 6, 7 and 12. Septins are polymerizing GTPases that can act as a scaffold forming hetero-oligomeric filaments required for cytokinesis and other cell cycle roles.**

  - **spermatogenesis**

  - **-(Greek,**

  - **genesis = origin, creation, generation) The term used to describe the process of diploid spermatagonia division and differentiation to form haploid spermatooza within the testis (male gonad). The process includes the following cellular changes: meiosis, reorganization of DNA, reduction in DNA content, reorganization of cellular organelles, morphological changes (cell shape). The final process of change in cell shape is also called spermiogenesis.**

  - **spermatogenesis**

  - **-(Greek,**

  - **genesis = origin, creation, generation) The maturation process of the already haploid spermatooza into the mature sperm shape and organization. This process involves reorganization of cellular organelles (endoplasmic reticulum, golgi apparatus, mitochondria), cytoskeletal changes (microtubule organization) and morphological changes (cell shape, acrosome and tail formation).**
spermatogonia - The cells located in the seminiferous tubule adjacent to the basal membrane that either divide and separate to renew the stem cell population, or they divide and stay together as a pair (Apr spermatogonia) connected by an intercellular cytoplasmic bridge to differentiate and eventually form spermatozoon.

spermatозоид head - Following spermiogenesis, the first region of the spermatozoon containing the haploid nucleus and acrosome. In humans, it is a flattened structure (5 µm long by 3 µm wide) with the posterior part of nuclear membrane forming the basal plate region. The human spermatozoon is about 60 µm long, actively motile and divided into 3 main regions (head, neck and tail).

spermatозоид neck - Following spermiogenesis, the second region of the spermatozoon attached to basal plate, transverse oriented centriole, contains nine segmented columns of fibrous material, continue as outer dense fibres in tail. In humans, it forms a short structure (1 µm). The human spermatozoon is about 60 µm long, actively motile and divided into 3 main regions (head, neck and tail).

spermatозоид tail - Following spermiogenesis, the third region of the spermatozoon that has a (head, neck and tail). The tail is also divided into 3 structural regions a middle piece, a principal piece and an end piece. In humans: the middle piece (5 µm long) is formed by axonema and dense fibres surrounded by mitochondria; the principal piece (45 µm long) fibrous sheath interconnected by regularly spaced circumferential hoops; the final end piece (5 µm long) has an axonema surrounded by small amount of cytoplasm and plasma membrane.

spermatogonial stem cells - (SSCs) The spermatogonia cells located beside the seminiferous tubule basal membrane that either divide and separate to renew the stem cell population, or they divide and stay together as a pair (Apr spermatogonia) connected by an intercellular cytoplasmic bridge to differentiate and eventually form spermatozoon.

sperm protein 56 - A component of the spermatozoon acrosomal matrix released to the sperm surface during capacitation.

External Links

External Links Notice - The dynamic nature of the internet may mean that some of these listed links may no longer function. If the link no longer works search the web with the link text or name.

- Salmon Lab Mitosis Movies (http://www.bio.unc.edu/faculty/salmon/lab/moviesmitosis.html)

2015 Course: Week 2 Lecture 1 Lecture 2 Lab 1 | Week 3 Lecture 3 Lecture 4 Lecture 2 Lab 2 | Week 4 Lecture 5 Lecture 6 Lab 3 | Week 5 Lecture 7 Lecture 8 Lab 4 | Week 6 Lecture 9 Lecture 10 Lab 5 | Week 7 Lecture 11 Lecture 12 Lab 6 | Week 8 Lecture 13 Lecture 14 Lab 7 | Week 9 Lecture 15 Lecture 16 Lab 8 | Week 10 Lecture 17 Lecture 18 Lab 9 | Week 11 Lecture 19 Lecture 20 Lab 10 | Week 12 Lecture 21 Lecture 22 Lab 11 | Week 13 Lecture 23 Lecture 24 Lab 12 | Projects: Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 | Students | Student Sharing | Moodle page (http://moodle.telt.unsw.edu.au/course/view.php?id=15814)

Glossary Links

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | Numbers | Symbols


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