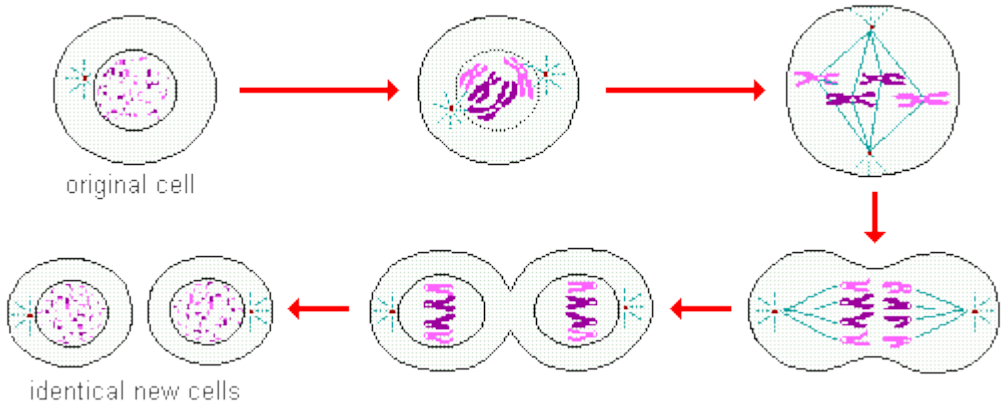
Cell Reproduction and Conception

Most human cells are frequently reproduced and replaced during the life of an individual. However, the process varies with the kind of cell. **Somatic**, or body cells, such as those that make up skin, hair, and muscle, are duplicated by **mitosis**. The **sex cells**, sperm and ova, are produced by **meiosis** in special tissues of male testes and female ovaries. Since the vast majority of our cells are somatic, mitosis is the most common form of cell replication.

Mitosis

The cell division process that produces new cells for growth, repair, and the general replacement of older cells is called mitosis. In this process, a somatic cell divides into two complete new cells that are identical to the original one. Human somatic cells go through the 6 phases of mitosis in 1/2 to 1 1/2 hours, depending on the kind of tissue being duplicated.



Six phases of mitosis

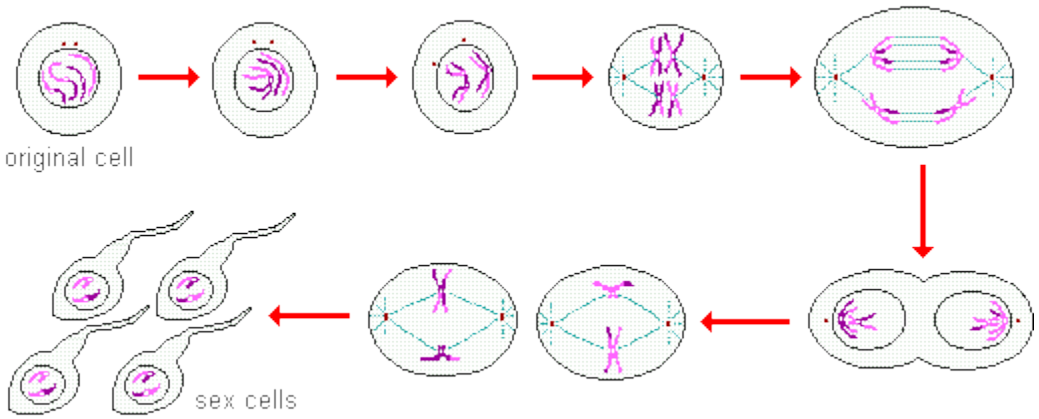
mitosis close up

Mitosis--video clip from Teachers' Domain
View in: *QuickTime* or *Windows Media Player*
(length = 1 min 35 secs)

Some human somatic cells are frequently replaced by new ones and other cells are rarely duplicated. Hair, skin, fingernails, taste buds, and the stomach's protective lining are replaced constantly and at a rapid rate throughout our lives. In contrast, brain and nerve cells in the central nervous system are rarely produced after we are a few months old. Subsequently, if they are destroyed later, the loss is usually permanent, as in the case of paraplegics. Liver cells usually do not reproduce after an individual has finished growing and are not replaced except when there is an injury. Red blood cells are also somewhat of an exception. While they are being constantly produced in our bone marrow, the specialized cells from which they come do not have nuclei nor do the red blood cells themselves.

Meiosis

Meiosis is a somewhat similar but more complex process than mitosis. This is especially true in females. While mitosis produces 2 daughter cells from each parent cell, meiosis results in 4 sex cells, or **gametes** in males and 1 in females. Unlike the cells created by mitosis, gametes are not identical to the parent cells. In males, meiosis is referred to as **spermatogenesis** because sperm cells are produced. In females, it is called **oögenesis** because ova, or eggs, are the main ultimate product. The illustration below shows the 8 phases of spermatogenesis.



Phases of spermatogenesis (i.e., meiosis in males)

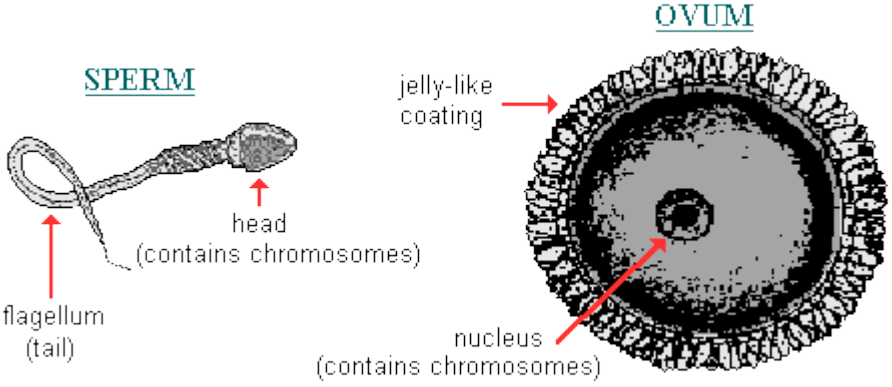
meiosis close up

How cells divide--side by side simulations of mitosis and meiosis
This link takes you to an external website. To return here, you must click the "back" button on your browser program.

Conception

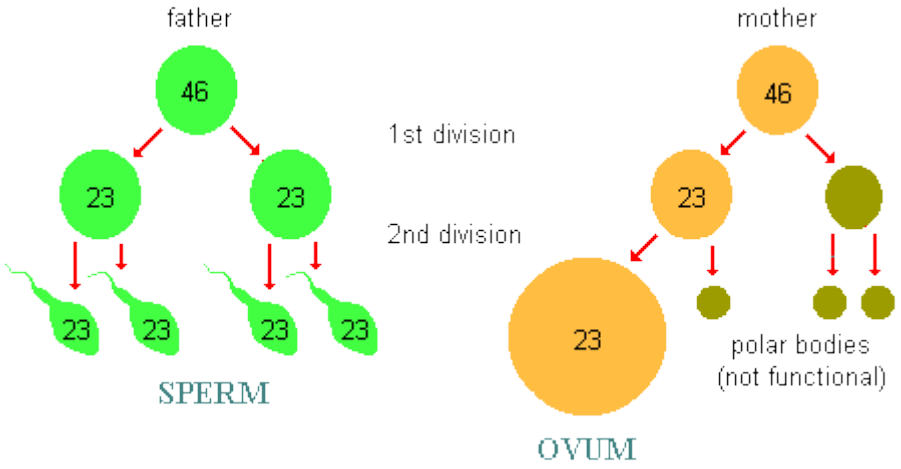
Sperm carries the father's chromosomes to the mother's **ovum** where they combine with her chromosomes at the time of conception. Sperm cells are microscopic, but ova may be large enough in some species to be visible with the naked eye. Human ova are about the diameter of a hair.

Human sex cells
(not drawn to the same scale)



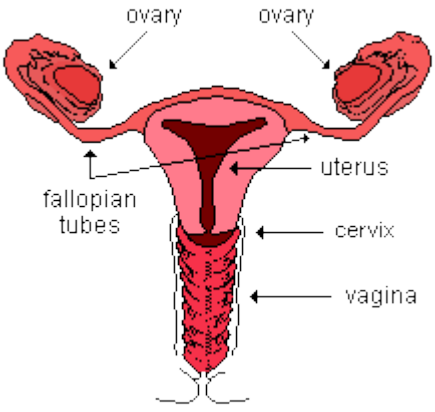
The two sequential division processes of meiosis culminate in the production of gametes with only half the number of chromosomes of somatic cells. As a result, human sperm and ova each have only 23 single-stranded chromosomes.

Summary of reduction division in meiosis



Human somatic cells, with their full set of 46 chromosomes, have what geneticists refer to as a diploid number of chromosomes. Gametes have a haploid number (23). When conception occurs, a human sperm and ovum combine their chromosomes to make a **zygote** (fertilized egg) with 46 chromosomes. This is the same number that the parents each had in their somatic cells. In doing this, nature is acting conservatively. Each generation inherits the same number of chromosomes. Without reducing their number by half in meiosis first, each new generation would have double the number of chromosomes in their cells as the previous one. Within only 15 generations, humans would have over 1½ million chromosomes per cell and would be a radically different kind of animal. In fact, when a zygote has an extra set of chromosomes, it usually is spontaneously aborted by the mother's reproductive system--it is a lethal condition.

The complete meiosis process in human males takes about 74 hours. Spermatogenesis usually begins at 12-13 years of age and continues throughout life. Several hundred million sperm cells are produced daily by healthy young adult males. Between 200 and 600 million sperm cells are normally released in each ejaculation. Since only one sperm cell is required for conception, this huge number would seem to be an extreme overkill. However, as many as 20% of sperm cells are likely to be defective and the female reproductive tract is hostile even to healthy ones--it is acidic and contains antibodies that seek out and destroy the sperm cells. Ejaculating large numbers of sperm at the same time is nature's way of overcoming these difficulties and increasing the likelihood that conception will take place. The number of sperm cells produced can be significantly diminished by psychological and physiological stress. Sperm count also progressively declines with age after reaching a peak, usually in the early 20's. In addition, the percentage of sperm that move randomly rather than in a straight line generally increases in older men. The result is a decrease in male fertility. The genes that are responsible for sperm production are in the Y sex chromosome. Unfortunately, the mutation rate for the Y chromosome is thought to be thousands of times higher than for those in other chromosomes. This may be a major cause of male infertility. As a result, genetic testing is beginning to be used to diagnose it.



Meiosis in human females is more complex. By the 5th month after conception, immature sex cells begin to develop in the fetal ovaries but stop at an early stage of meiosis (after prophase I). They remain in this precursor egg cell, or **primary oöcyte**, phase until puberty when hormones cause a resumption of meiosis for one to several cells each month. They proceed to the 1st and 2nd reduction divisions and once again stop developing. At this stage they are **secondary oöcytes**. When a secondary oöcyte is finally released from the ovaries into the fallopian tube (during ovulation), the egg still has not completed the last stage of meiosis. That happens only at conception as a result of chemical changes that occur when the main part of a sperm cell enters the ovum.

Human female reproductive system

Virtually all (99.9%) sex cells in a woman's ovaries never develop beyond the primary oöcyte stage and eventually are reabsorbed by her body. By 20 weeks after conception, there are approximately 7,000,000 primary oöcytes. All but about 1,200,000 are lost by birth. At puberty, there are only around 400,000 of them remaining. Throughout life, there is a constant decline in the number of potential eggs. Each time one is successfully ovulated, as many as 2000 are lost. Normally, women have on average 11-14 ovulations per year for 33-36 years. This means that less than 500 secondary oöcytes usually are produced out of the store of hundreds of thousands of primary oöcytes. The actual number of ovulations is highly variable and often much lower since the process is governed by hormones and ultimately other factors including psychological stress, nutrition, physical activity, and pathological conditions. The fact that women rarely have more than a few children is evidence that only a small fraction of the successfully ovulated eggs are fertilized and become viable zygotes. Beginning about age 27, a woman's fertility progressively declines. Around 35-37 years old, the decline becomes much steeper and the chances of conception significantly lower. By the early 50's, most women begin the transition to menopause when they stop ovulating altogether. The temporary cessation of ovulation and subsequent infertility can occur much earlier in life as a result of reduced blood estrogen levels caused by excessive physical activity. This is very likely the reason that roughly a quarter of American women athletes in high school and college cease having menstrual periods. It also results in a significant decrease in their bone density.

NOTE: Humans may be the only animal species in which females now normally live for many years following menopause. Freed from having more children themselves, human grandmothers are in a position to assist their own daughters and sons in rearing their offspring. This potentially increases the chances that grandchildren will survive, thereby giving our species an advantage over other animals in the competition for survival. However, people rarely lived beyond menopause until a little over a century ago when modern medicine and other technological advances made it possible. Prior to that time, we were more often like other animals in that most of us succumbed to disease, accidents, or predators before middle age and menopause.

NOTE: On-going research suggests that it may be possible within a few years to return fertility to post menopausal women by stimulating stem cells in their ovaries to produce new eggs.

Study Suggests Way To Create New Eggs In Women--National Public Radio audio report on February 27, 2012. To return here, you must click the "back" button on your browser program. (4 mins, 3 secs)

When human sexual intercourse occurs, it takes about 5 minutes for sperm to reach the upper end of the fallopian tubes where conception usually takes place. Of the several hundred million sperm cells that enter a vagina, rarely do more than a few hundred successfully pass through the cervix and uterus. Only about 100 reach the upper end of the fallopian tubes. Sperm cells are guided over this path mostly by heat

sensing. The upper ends of the fallopian tubes are about two degrees warmer than the lower ends. Secondary oöcytes secrete chemicals that also may guide sperm cells to them when they are in close proximity. Usually, only the most viable sperm cells reach the secondary oöcytes and play their part in conception. Those sperm that fail in this competition are often genetically abnormal. The endurance test that they must go through in the female reproductive tract is nature's way of eliminating these poorer specimens.

Among humans, fertilization usually occurs within a day after ovulation. It takes about 4 days for secondary oöcytes to pass through the fallopian tube in their journey to the uterus. Conception must occur early in this process. Sperm usually can remain viable for up to 48 hours in the female reproductive tract, but secondary oöcytes remain viable for only about 24 hours after they have left the ovaries. This means that sexual intercourse must occur from a few days before to one day after ovulation if conception is desired. In most non-human mammals, birds, reptiles, fish, and insects, fertilization is made more likely by the fact that females are sexually receptive only around the time of ovulation. This period of female sexual receptivity is called **estrus**. In most species, it is common for all females to have their ovulations around the same time of year. This reproductive synchronization results in a common mating season. In humans and some other primates, sexuality is far less related to the timing of ovulation. Among these species, there is no mating season. More precisely, the entire year is a mating season since they have a more or less chronic interest in sex. This is another way in which nature has chosen to increase the likelihood of conception.

Half of the sperm cells produced normally carry the X-chromosome and half have the Y-chromosome. Subsequently, we would expect that 50% of human babies would be males and 50% females, but this usually is not the case. The ratio of male to female newborns in the U.S. and most of the world is 105-110 males to 100 females. The ratio of males to females at conception is generally even higher than it is at birth. This is fortunate in the long run for society because male spontaneous abortions and infant mortality rates are higher. In addition, males are more likely to die from accidents and combat as teenagers and young men. Males in developed nations who survive to adulthood also can expect to die at a younger age than women.

Male-Female Ratios in the United States

	Males	Females
at conception	130-150	100
at birth	105-110	100
at age 20	98	100
at age 65+	68	100

Current cultural practices in China and India result in even higher rates of male births. Since 1979, China has had a national policy of allowing parents to have only one child in order to reduce population growth. A traditional preference for male children and the ready availability of ultrasound technology has led to large numbers of abortions of female fetuses. This occurs despite the fact that abortions for the purpose of preventing the birth of female children is illegal. There are now 119 boys born for every 100 girls in China, and in some regions the ratio is as high as 144 to 100. A consequence of this practice is the growing scarcity of marriageable women. As of the 2005 census, there were 32 million more young men than women in China. While India does not have a one child policy, it is facing a similar problem because of the selective abortion of female fetuses, especially in the more prosperous states of North India. This is driven by the economic difficulty of raising large families and the preference for male children. The huge excess of marriageable men in China and India could be socially and politically explosive in the near future.

In societies that encourage a form of marriage in which one man has more than one wife at the same time (polygyny), higher numbers of female children are usually born than in the predominantly monogamous nations. Why this reverse birth ratio pattern occurs is not entirely understood. However, it is very likely

connected with the fact that each wife has less frequent sexual intercourse. Girls are more likely to be conceived when conception is close to the time of ovulation. When there is intercourse at other times as well, the sperm cells are more likely to be waiting for ovulation at the upper end of the fallopian tubes. They do not have as far to go to reach the egg.

 Life's Greatest Miracle--PBS Nova series video on conception, gestation, and birth
This link takes you to an external website. To return here, you must click the "back" button on your browser program. (8 parts of 4-10 mins each)

Why Twins?

Multiple births at the same time are rare for humans and most other primate species. Having fraternal, but not identical, twins apparently runs in family lines, and is also somewhat more likely for women over age 30.

Fraternal twins may look similar but are not genetically identical. In fact they are no more identical than any brother or sister. They share their mother's uterus during gestation but come from two different eggs fertilized with different sperm. Subsequently, they are called **dizygotic twins**  . In contrast, identical twins are mostly identical genetically because they result from one zygote splitting into two or more separate ones within a few days after conception. As a consequence, they are called **monozygotic twins**  . If the division of the original zygote does not occur until the 9th to the 12th day after conception, the monozygotic twins are likely to be **mirror twins**. That is, they will have small mirror image differences internally and externally. For instance, one may be left handed and the other right handed. Likewise, the cowlick in their hair at the back of the head will be on opposite sides. If the division of the zygote occurs after day 13, the monozygotic twins are likely to be born conjoined.

Any differences between monozygotic twins later in life are mostly the result of environmental influences rather than genetic inheritance. However, monozygotic twins may not share all of the same sequences of mitochondrial DNA. This is due to the fact that the mitochondria in a cell may have somewhat different versions of DNA, and the mitochondria can be dispersed unequally when a zygote fissions. Female monozygotic twins can also differ because of differences between them in X-chromosome inactivation. Subsequently, one female twin can have an X-linked condition such as muscular dystrophy and the other twin can be free of it.

NOTE: X-chromosome inactivation in females was described at the end of the first topic section of this tutorial ("Basic Cell Structures") and mitochondrial DNA is described in the last topic section ("Molecular Level of Genetics").

There has been at least one recorded instance of twins who are identical on their mother's side but share only half of their father's genes. These "semi-identical" twins result from two sperm cells fertilizing the same egg. This double fertilization of an egg apparently occurs in about 1% of human conceptions. In most cases, the embryo is not viable and dies.

Dizygotic twins can also be produced when a woman has sexual intercourse with more than one man around the time she is ovulating. If multiple viable eggs are released from her ovaries, each can be fertilized by sperm from a different man. This is referred to as **heteropaternity**.

Why Hermaphrodites?

Normally in humans one sperm cell combines its chromosomes with those of one ovum at conception and that in turn develops into a single embryo that will become a fetus. Very rarely, however, two zygotes fuse and become a single embryo. If it survives gestation, a baby will be born who is a true **chimera**--it is genetically two "people" in one body. If those two "people" are not the same gender, the baby will likely be a hermaphrodite--it will have both male and female sex organs and other body tissues. Some researchers believe that the frequency of chimeras being born will be increasing as in vitro fertilization becomes more common since two or more embryos are usually placed in the uterus with this procedure.

NEWS: On January 16, 2005, a 66 year old Romanian woman named Adriana Iliescu gave birth to a daughter. This makes her the oldest woman to become pregnant and deliver a live baby. She was implanted with a fertilized egg from a healthy younger woman. The baby was 6 weeks premature and weighed only 1.4 kilograms (3.1 pounds), which is less than half the normal newborn weight. Two other fetuses died during the pregnancy (News at Nature.com, January 17, 2005).

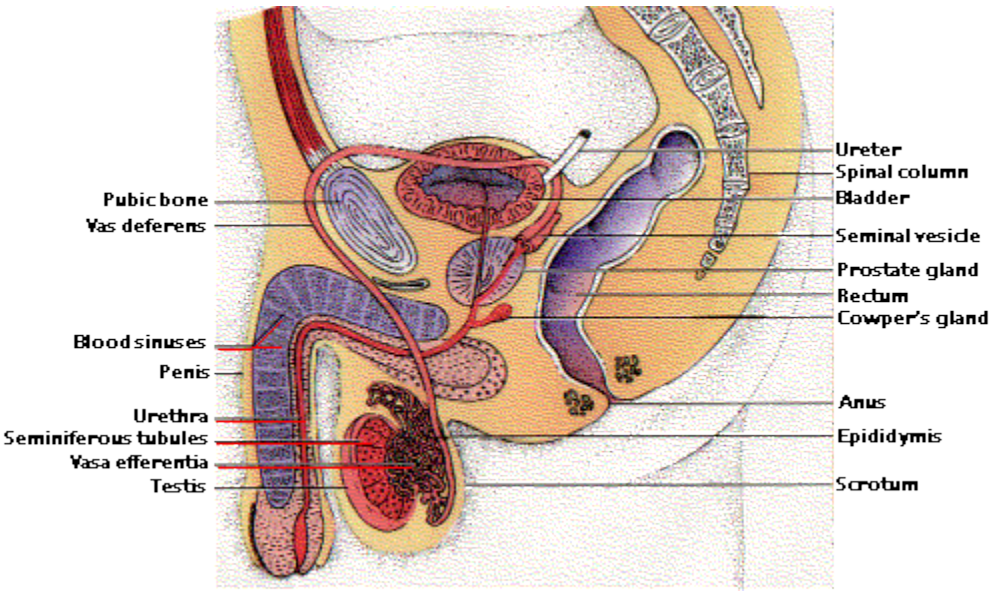
NEWS: In the August 23, 2009 issue of Biology Letters, Kristen Navara of the University of Georgia presented the results of a 202 nation survey of data on male to female ratios at birth. She noted that there is a skewing of sex ratios that corresponds to latitude. In temperate and subarctic latitudes, there are slightly more boys born compared to tropical latitudes. Navara said that these differences were independent of cultural practices and the socio-economic status of families.

Previous Topic | Return to Menu | Practice Quiz | Next Topic

- production of sperm
- delivery of these to the reproductive tract of the female.

Sperm production — spermatogenesis — takes place in the **testes**.

Each testis is packed with **seminiferous tubules** (laid end to end, they would extend more than 20 meters) where spermatogenesis occurs.



Spermatogenesis

The walls of the seminiferous tubules consist of diploid spermatogonia, stem cells that are the precursors of sperm.

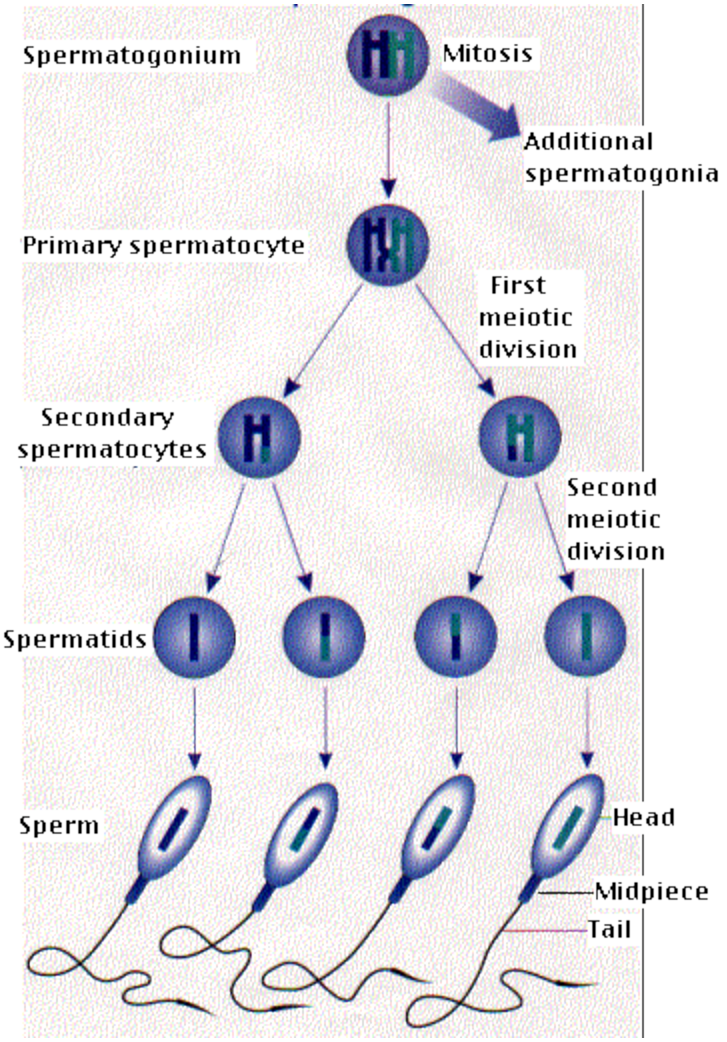
Spermatogonia

- divide by mitosis to produce more spermatogonia or
- differentiate into **spermatocytes**.

Meiosis of each spermatocyte produces 4 haploid **spermatids**. This process takes over three weeks to complete.

Then the spermatids differentiate into sperm, losing most of their cytoplasm in the process.

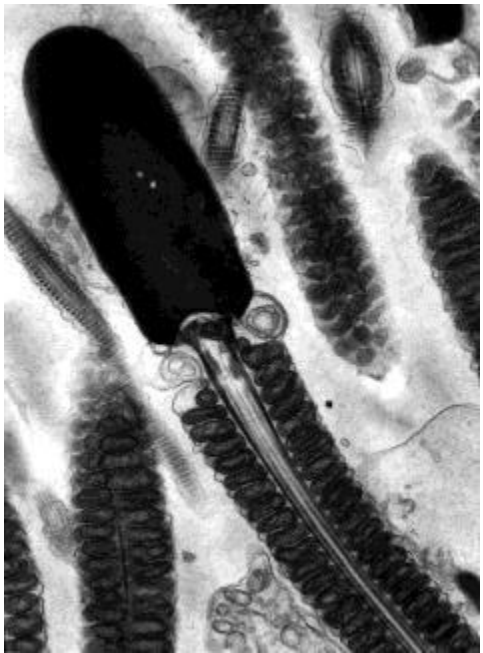
For simplicity, the figure shows the behavior of just a single pair of homologous chromosomes with a single crossover. With 22 pairs of autosomes and an average of two crossovers between each pair, the variety of gene combinations in sperm is very great.



Sperm

Sperm cells are little more than flagellated nuclei. Each consists of

- a head, which has
  - an **acrosome** at its tip and
  - contains a haploid set of chromosomes in a compact, inactive, state.
- a **midpiece** containing mitochondria and a single centriole
- a **tail** which is a flagellum.



This electron micrograph (courtesy of Dr. Don W. Fawcett and Susumu Ito) shows the sperm cell of a bat. Note the orderly arrangement of the mitochondria. They supply the ATP to power the whiplike motion of the tail.

An adult male manufactures over 100 million sperm cells each day. These gradually move into the **epididymis** where they undergo further maturation. The acidic environment in the epididymis keeps the mature sperm inactive.

In addition to making sperm, the testis is an **endocrine gland**. Its principal hormone, **testosterone**, is responsible for the development of the secondary sex characteristics of men such as the beard, deep voice, and masculine body shape. **Testosterone is also essential for making sperm.**

Link to more on testosterone.

Testosterone is made in the **interstitial cells** (also called Leydig cells) that lie between the seminiferous tubules.

LH

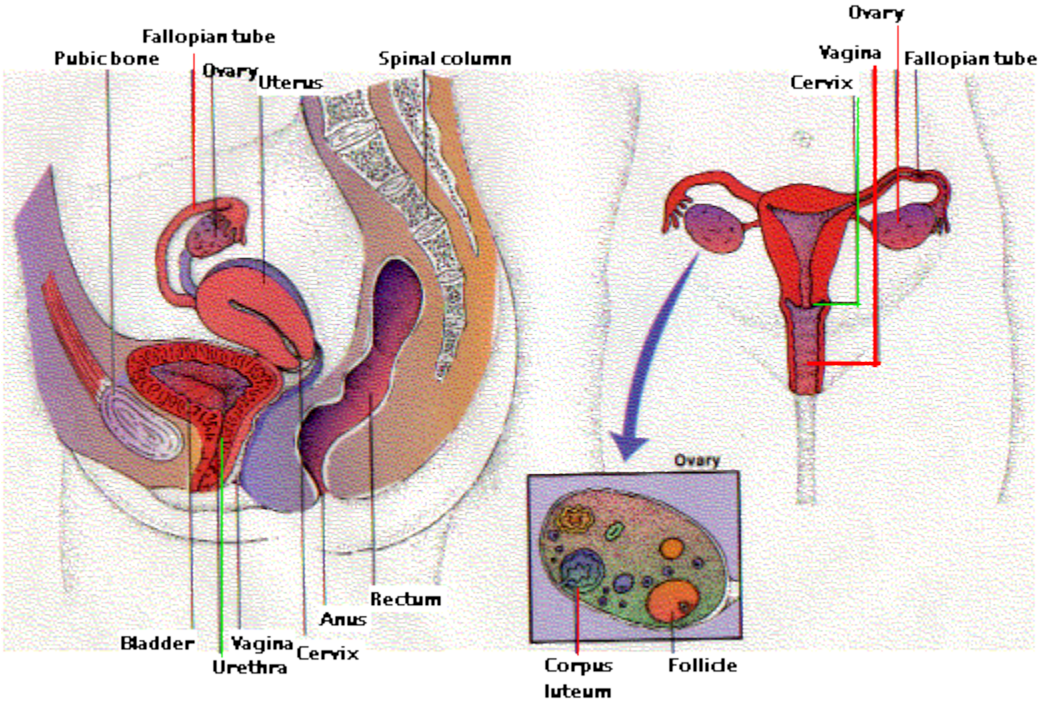
Interstitial cells are, in turn, the targets for a hormone often called interstitial cell stimulating hormone (**ICSH**). It is a product of the anterior lobe of the pituitary gland. However, ICSH is identical to the luteinizing hormone (**LH**) found in females, and I prefer to call it LH.

FSH

Follicle-stimulating hormone (also named for its role in females) acts directly on spermatogonia to stimulate sperm production (aided by the LH needed for testosterone synthesis). [Discussion]

Sex Organs of the Human Female

The responsibility of the female mammal for successful reproduction is considerably greater than that of the male.



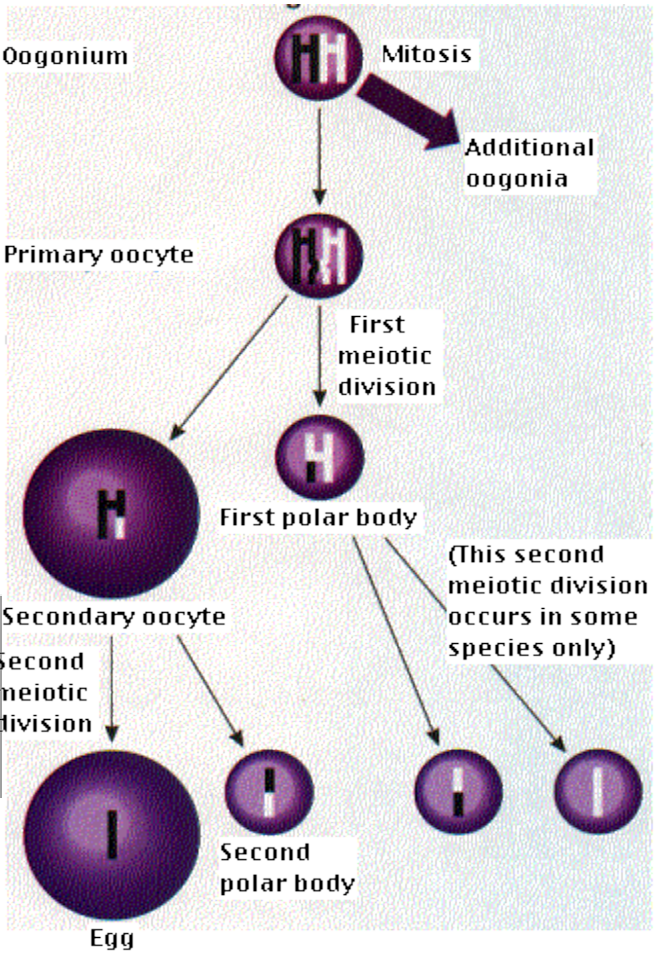
She must

- manufacture eggs
- be equipped to receive sperm from the male
- provide an environment conducive to fertilization and implantation
- nourish the developing baby not only before birth but after.

Oogenesis

Egg formation takes place in the **ovaries**.

In contrast to males, the initial steps in egg production occur prior to birth. Diploid stem cells called **oogonia** divide by mitosis to produce more oogonia and **primary oocytes**. By the time the fetus is 20 weeks old, the process reaches its peak and all the oocytes that she will ever possess (~4 million of them) have been formed (*). By the time she is born, only about 1 million of these remain (the others eliminated by apoptosis). Each has begun the first steps of the first meiotic division stopping at the diplotene stage of meiosis I.



No further development occurs until years later when the girl becomes sexually mature. Then the primary oocytes recommence their development, usually one at a time and once a month.

*Recent evidence in both mice and young women show the presence of oogonial stem cells that in vitro can develop into immature oocytes. Whether these can go on to develop enough to be fertilized AND whether such stem cells naturally produce new eggs in young women remains to be seen.

The primary oocyte grows much larger and completes meiosis I, forming a large **secondary oocyte** and a small **polar body** that receives little more than one set of chromosomes. Which chromosomes end up in the egg and which in the polar body is entirely a matter of chance.

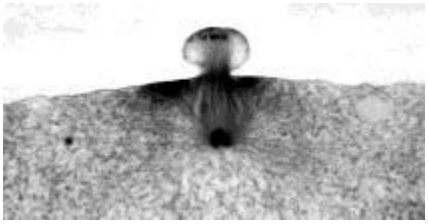
In humans (and most vertebrates), the first polar body does not go on to meiosis II, but the secondary oocyte does proceed as far as **metaphase** of meiosis II and then stops.

Only if **fertilization** occurs will meiosis II ever be completed. Entry of the sperm restarts the cell cycle

- breaking down MPF (M-phase promoting factor) and
- turning on the anaphase-promoting complex (APC).

Completion of meiosis II converts the secondary oocyte into a fertilized egg or zygote (and also a second polar body).

As in the diagram for spermatogenesis, the behavior of the chromosomes is greatly simplified.



The photomicrograph (courtesy of Turtox) shows polar body formation during oogenesis in the whitefish. Even allowing for the fact that fish eggs are larger than mammalian eggs, you can readily see how the polar body gets little more than one set of chromosomes.

These events take place within a **follicle**, a fluid-filled envelope of cells surrounding the developing egg.

The ripening follicle also serves as an **endocrine gland**. Its cells make a mixture of steroid hormones collectively known as **estrogen**. Estrogen is responsible for the development of the secondary sexual characteristics of a mature woman, e.g.,

- a broadening of the pelvis
- development of the breasts
- growth of hair around the genitals and in the armpits
- development of adipose tissue leading to the more rounded body contours of adult women.

Estrogen continues to be secreted throughout the reproductive years of women During this period, it plays an essential role in the monthly **menstrual cycle**.

Link to a discussion of the **menstrual cycle** and the hormones that regulate it.

There is growing evidence that in mice oocytes can continue to be produced throughout life (from germline stem cells in the bone marrow). It remains to be seen if that will turn out to be true for humans.

Ovulation

Ovulation occurs about two weeks after the onset of menstruation. In response to a sudden surge of LH, the follicle ruptures and discharges a secondary oocyte. This is swept into the open end of the **fallopian tube** and begins to move slowly down it.

Several sexually-transmitted diseases (STDs), especially gonorrhea and infections by chlamydia can cause scarring and blocking of the tubes and are a major cause of infertility.
In tubal ligation, the fallopian tubes are surgically cut and their ends tied to prevent pregnancy.

Copulation and Fertilization

For fertilization to occur, sperm must be deposited in the vagina within a few (5) days before or on the day of ovulation. Sperm transfer is accomplished by copulation. Sexual excitation dilates the arterioles supplying blood to the penis. Blood accumulates in three cylindrical spongy sinuses that run lengthwise through the penis. The resulting pressure causes the penis to enlarge and erect and thus able to penetrate the vagina.

Movement of the penis back and forth within the vagina causes sexual tension to increase to the point of **ejaculation**. Contraction of the walls of each **vas deferens** propels the sperm along. Fluid is added to the sperm by the **seminal vesicles**, Cowper's glands, and the **prostate gland**. [View] These fluids provide

- a source of energy (fructose)
- an alkaline environment to activate the sperm, and
- perhaps in other ways provide an optimum chemical environment for them.

The mixture of sperm and accessory fluids is called **semen**. It passes through the **urethra** and is expelled into the vagina.

Physiological changes occur in the female as well as the male in response to sexual excitement, although these are not as readily apparent. In contrast to the male, however, such responses are not a prerequisite for copulation and fertilization to occur.

Once deposited within the vagina, the sperm proceed on their journey into and through the uterus and on up into the fallopian tubes. It is here that fertilization may occur if an "egg" is present (strictly speaking, it is still a secondary oocyte until after completion of meiosis II).

Although sperm can swim several millimeters each second, their trip to and through the fallopian tubes may be assisted by muscular contraction of the walls of the uterus and the tubes. The trip is fraught with heavy mortality. An average

human ejaculate contains over one hundred million sperm, but only a few dozen complete the journey, arriving within 15 minutes of ejaculation. And of these, only one will succeed in fertilizing the egg.

Sperm swim towards the egg by chemotaxis following a gradient of progesterone secreted by cells surrounding the egg. Progesterone opens CatSper ("cation sperm") channels in the plasma membrane surrounding the anterior portion of the sperm tail. This allows an influx of Ca^{2+} ions which causes the flagellum to beat more rapidly and vigorously.

Fertilization begins with the binding of a sperm head to the glycoprotein coating of the egg (called the **zona pellucida**). Exocytosis of the **acrosome** at the tip of the sperm head releases enzymes that digest a path through the zona and enable the sperm head to bind to the plasma membrane of the egg. Fusion of their respective membranes allows the entire contents of the sperm to be drawn into the cytosol of the egg. (Even though the sperm's mitochondria enter the egg, they are almost always destroyed — by autophagy — and do not contribute their genes to the embryo. So human mitochondrial DNA is almost always inherited from mothers only.)

Within moments, enzymes released from the egg cytosol act on the zona making it impermeable to the other sperm that arrive.

Soon the nucleus of the successful sperm enlarges into the **male pronucleus**. At the same time, the egg (secondary oocyte) completes meiosis II forming a **second polar body** and the **female pronucleus**.

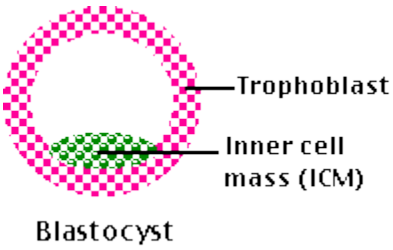
The male and female pronuclei move toward each other while duplicating their DNA in S phase. Their nuclear envelopes disintegrate. A spindle is formed (following replication of the sperm's centriole), and a full set of dyads assembles on it. The fertilized egg or **zygote** is now ready for its first mitosis. When this is done, 2 cells — each with a diploid set of chromosomes — are formed.

In sea urchins, at least, the block to additional sperm entry and the fusion of the pronuclei are triggered by nitric oxide generated in the egg by the sperm acrosome. [Link]

Pregnancy

Development begins while the fertilized egg is still within the **fallopian tube**. Repeated mitotic divisions produces a solid ball of cells called a **morula**. Further mitosis and some migration of cells converts this into a hollow ball of cells called the **blastocyst**. Approximately one week after fertilization, the blastocyst embeds itself in the thickened wall of the uterus, a process called **implantation**, and pregnancy is established.

The blastocyst produces two major collections of cells:



- Three or four blastocyst cells develop into the **inner cell mass**, which will form
  - 3 extraembryonic membranes: **amnion**, **yolk sac**, and (a vestigial) **allantois** and
  - in about 2 months, become the fetus and, ultimately, the baby.
- The remaining 100 or so cells form the **trophoblast**, which will develop into the **chorion** that will go on to make up most of the **placenta**. All the extraembryonic membranes play vital roles during development but will be discarded at the time of birth.

The placenta grows tightly fused to the wall of the uterus. Its blood vessels, supplied by the fetal heart, are literally bathed in the mother's blood. Although there is normally no mixing of the two blood supplies, the placenta does facilitate the transfer of a variety of materials between the fetus and the mother.

- receiving food
- receiving oxygen and discharging carbon dioxide
- discharging urea and other wastes

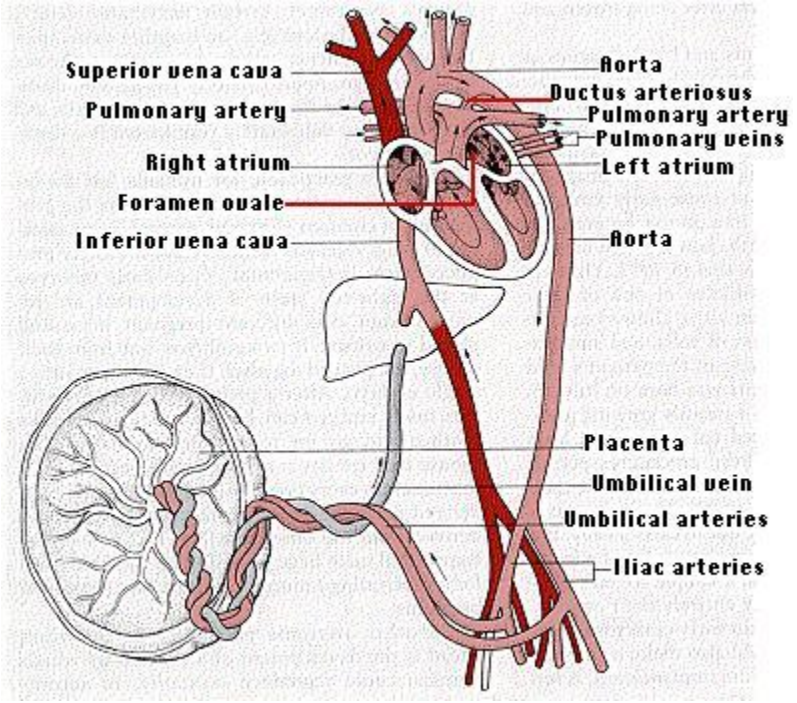
- receiving **antibodies** (chiefly of the IgG class). These remain for weeks after birth, protecting the baby from the diseases to which the mother is immune.

But the placenta is not simply a transfer device. Using raw materials from the mother's blood, it synthesizes large quantities of proteins and also some hormones.

Link to discussion of the placenta as an endocrine gland.

The metabolic activity of the placenta is almost as great as that of the fetus itself.

The **umbilical cord** connects the fetus to the placenta. It receives deoxygenated blood from the iliac arteries of the fetus and returns oxygenated blood to the liver and on to the inferior vena cava.



Because its lungs are not functioning, circulation in the fetus differs dramatically from that of the baby after birth. While within the uterus, blood pumped by the right ventricle bypasses the lungs by flowing through the **foramen ovale** and the **ductus arteriosus**.

Although the blood in the placenta is in close contact with the mother's blood in the uterus, intermingling of their blood does not normally occur. However, some of the blood cells of the fetus usually do escape into the mother's circulation — where they have been known to survive for decades. This raises the possibility of doing **prenatal diagnosis** of genetic disorders by sampling the mother's blood rather than having to rely on the more invasive procedures of amniocentesis and chorionic villus sampling (CVS).

Fragments of fetal DNA (~ 300 bp long) from apoptotic cells of the placenta are also found in the mother's plasma as early as 5 weeks after implantation. These can be tested for various forms of aneuploidy, e.g. the trisomy 21 of Down syndrome [More].

Far rarer is the leakage of mother's blood cells into the fetus. However, it does occur. A few pregnant women with leukemia or lymphoma have transferred the malignancy to their fetus. Some babies have also acquired melanoma from the transplacental passage of these highly-malignant cells from their mother.

During the first 2 months of pregnancy, the basic structure of the baby is being formed. This involves cell division, cell migration, and the differentiation of cells into the many types found in the baby. During this period, the developing baby — called an **embryo** — is very sensitive to anything that interferes with the steps involved. Virus infection of the mother, e.g., by rubella ("German measles") virus or exposure to certain chemicals may cause malformations in the developing embryo. Such agents are called **teratogens** ("monster-forming"). The tranquilizer, thalidomide, taken by many pregnant European women between 1954 and 1962, turned out to be a potent teratogen and was responsible for the birth of several thousand deformed babies.

After about two months, all the systems of the baby have been formed, at least in a rudimentary way. From then on, development of the **fetus**, as it is now called, is primarily a matter of growth and minor structural modifications. The fetus is less susceptible to teratogens than is the embryo.

Pregnancy involves a complex interplay of **hormones**. These are described in a separate page. [Link to it.]

The placenta is an allograft

One of the greatest unsolved mysteries in immunology is how the placenta survives for 9 months without being rejected by the mother's immune system. Every cell of the placenta carries the father's genome (a haploid set of his chromosomes); including one of his #6 chromosomes where the genes for the **major histocompatibility antigens** (HLA) are located.

One partial exception: none of the genes on the father's X chromosome are expressed. While X-chromosome inactivation is random in the cells of the fetus, it is NOT random in the cells of the trophoblast. In every cell of the trophoblast — and its descendants — it is the paternal X chromosome that is inactivated. [Discussion of X-chromosome inactivation.] But this does not solve our problem because the genes for all the major histocompatibility antigens are located on chromosome 6, which is not inactivated.
Discussion of the human major histocompatibility complex (MHC)

Thus the placenta is immunologically as foreign to the mother as a kidney transplant would be.

Yet it thrives.

Despite a half-century of research, the mechanism for this immunologically privileged status remains uncertain. But one thing is clear:

The mother is **not** intrinsically tolerant of the father's antigens.

Some evidence:

- She will promptly reject a skin transplant from the father.
- She develops antibodies against his histocompatibility antigens expressed by the fetus. In fact, women who have borne several children by the same father are often excellent sources of anti-HLA serum for use in tissue typing.

So what accounts for the phenomenon? Some possibilities:

- The placenta does not express class II histocompatibility antigens.

Discussion of the role of class II antigens in immunity.

- Nor does it express the strongly-immunogenic class I histocompatibility antigens (HLA-A, HLA-B). It does express HLA-C, but this is only weakly immunogenic.
- The cells of the placenta secrete progesterone, which is immunosuppressive.
- In lab rats the embryos (and the mother's endometrium) secrete corticotropin-releasing hormone (CRH). This hormone induces the expression of Fas ligand (**FasL**) on the cells of the placenta. Activated T cells express **Fas** so any threatening T cells would commit suicide by apoptosis when they encounter FasL on their target.

Link to more of the story of the role of Fas and FasL in apoptosis. (but **note:** the example you will see is the **reverse** of the story here; that is, the cytotoxic T cell is using its own FasL to kill a target cell that is expressing Fas but **not** FasL.)

- In laboratory mice the cells of the placenta degrade the amino acid tryptophan. Tryptophan is essential for T-cell function. When mice are treated with an inhibitor of the Trp-degrading enzyme, their fetuses are promptly aborted by the action of the mother's lymphocytes. (D. H. Munn, et. al., **Science**, **281:** 1191, 21 Aug 1998.)

- In mice, expression of genes encoding cytokines needed to attract effector T cells (e.g., CTLs) into a tissue is suppressed in the cells of the placenta.
- Perhaps most important of all is the increased production in the mother of immunosuppressive **regulatory T cells** (Treg).
    - Depletion of Treg cells in pregnant mice leads to spontaneous abortion while
    - injection of Treg cells into mice that are otherwise prone to abortion enables them to carry their fetuses to term.
    - In humans, the number of Treg cells rises during pregnancy (in the fetus as well as the mother).

Assisted Reproductive Technology ("ART")

On July 25, 2010 Louise Brown celebrated her 32th birthday. She was the first of what today number some four million (worldwide) "test tube babies"; that is, she developed from an egg that was fertilized outside her mother's body — the process called **in vitro fertilization** (**IVF**).

In Vitro Fertilization (IVF)

IVF involves

- harvesting mature eggs from the mother. This is not an easy process. The mother must undergo hormonal treatments to produce multiple eggs, which then must be removed (under anesthesia) from her ovaries.
- harvesting sperm from the father. Harvesting is usually no problem, but often the sperm are defective in their ability to fertilize (so setting the stage for ICSI);
- mixing sperm and eggs in a culture vessel ("in vitro");
- culturing the fertilized eggs for several days until they have developed to at least the 8-cell stage;
- placing two or more of these into the mother's uterus (which her hormone treatments have prepared for implantation);
- keeping one's fingers crossed — only about one-third of the attempts result in a successful pregnancy)

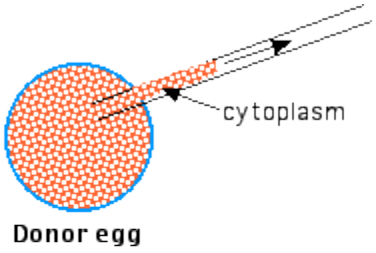
Intracytoplasmic Sperm Injection (ICSI)

Successful IVF assumes the availability of healthy sperm. But many cases of infertility arise from defects in the father's sperm. Often these can be overcome by directly injecting a single sperm into the egg.

In the U.S. today, some two-thirds of ART procedures employ ICSI (even though as many as half of these do not involve male infertility).

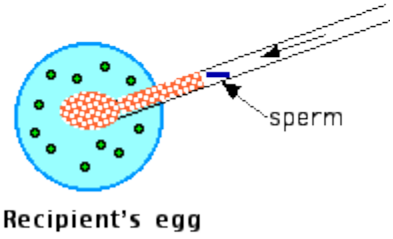
Ooplasmic Transfer

Infertility in some cases may stem from defects in the cytoplasm of the mother's egg. To circumvent these, cytoplasm can be removed from the egg of a young, healthy woman ("Donor egg") and injected — along with a single sperm — into the prospective mother's egg.



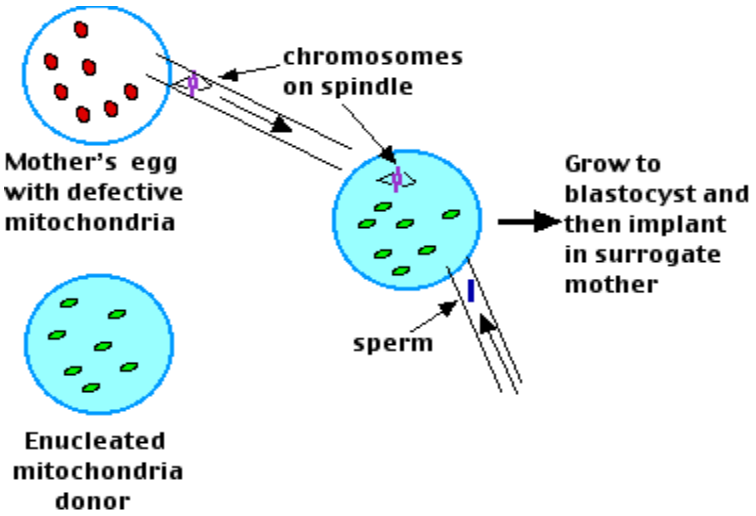
Although a few healthy children have been born following ooplasmic transfer, the jury is still out on its safety, and it is not approved for use in the U.S.

One reason for concern is that ooplasmic transfer results in an egg carrying both the mother's mitochondria and mitochondria from the donor (in normal fertilization, all the mitochondria in the father's sperm are destroyed in the egg). This condition — called **heteroplasmy** — creates a child having two different mitochondrial DNA genomes in all



of its cells.

In rare, but important, cases, the defect in the prospective mother's cytoplasm is the result of her having mitochondria with a mutant gene (link to examples]. Ooplasmic transfer is of no help in these cases because the fertilized egg will still contain a preponderance of the mother's defective mitochondria. But researchers in Oregon reported in the 17 September 2009 issue of **Nature** that they had been able to produce 4 healthy rhesus monkeys with no mitochondria from their biological mother.



Their procedure:

- Remove the spindle with all its attached chromosomes from the mother's oocyte at metaphase II of meiosis. They managed to do this without any of her mitochondria being withdrawn as well.
- Enucleate the oocyte of the mitochondria donor and then insert the mother's chromosomes — still attached to the spindle — into it. Then inject a sperm from the father.
- Allow the fertilized egg to develop into a blastocyst.
- Implant this in the uterus of a surrogate mother.
- The result: 4 healthy babies each with the nuclear genes of their mother and father but none of the mitochondria of their mother.

If this technique could be applied to humans, it would allow women carrying defective mitochondria to bear babies free of the ailment.

The Upside of ART

- It has allowed some four million previously-infertile couples to have children.
- It permits screening (on one cell removed from the 8-celled morula) for the presence of genetic disorders — thus avoiding starting a pregnancy if a disorder is found.

  Link to a discussion.

- One can use frozen sperm allowing fatherhood for a man who is no longer able to provide fresh sperm.
- Because a number of morulas are created, the extras can be frozen, stored, and used later
  - if the initial attempt fails (the prospective mother must still receive hormones to prepare her uterus for implantation and the success rate is lower with thawed morulas).
  - Where regulations permit, the extras can be used as a source of embryonic stem (ES) cells.

  Discussion

The Downside of ART

- Although improving, the success rate is still sufficiently low (~35%) that the process often has to be repeated (which is physically demanding as well as very expensive).

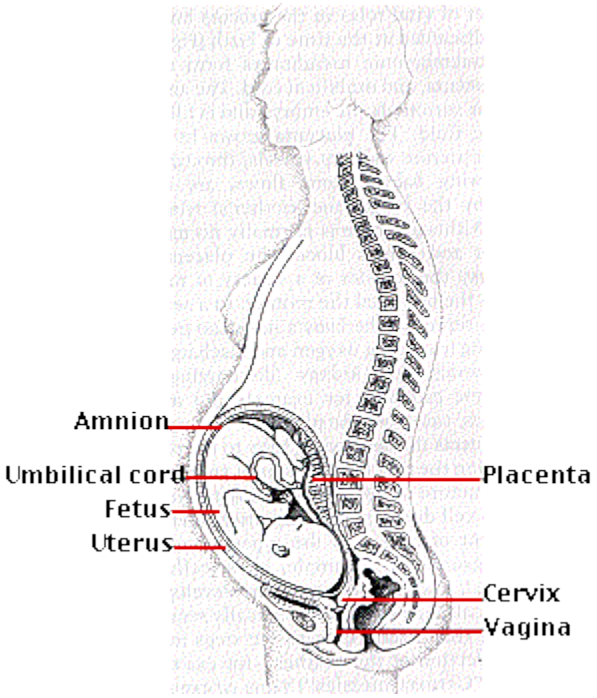
- Because several morulas are usually transferred, multiple births are common (about 50%), and as is the case with most multiple births, the babies are born early and weigh less. To reduce the number of twins, triplets, etc., more ART centers are turning to **"single-embryo transfer"** (SET). Some ART centers find that they can increase the success rate — and thus rely more on SET — by culturing the morulas for 5–6 days, instead of the usual 2–3 days, before transferring them (by now they have become blastocysts) to the mother.
- The risk of birth defects may be increased slightly (from ~6% in "normal" pregnancies to ~8% in ART pregnancies).
- ART procedures in experimental animals often result in a failure of correct gene imprinting. Whether this will pose a problem for humans remains to be seen.

Birth and Lactation

Exactly what brings about the onset of labor is still not completely understood. Probably a variety of integrated hormonal controls are at work.

Link to a discussion of hormones involved in birth and lactation.

The first result of labor is the opening of the cervix. With continued powerful contractions, the amnion ruptures and the amniotic fluid (the "waters") flows out through the vagina. The baby follows, and its umbilical cord can be cut.



The infant's lungs expand, and it begins breathing. This requires a major switchover in the circulatory system. Blood flow through the umbilical cord, ductus arteriosus, and foramen ovale ceases, and the adult pattern of blood flow through the heart, aorta, and pulmonary arteries begins. In some infants, the switchover is incomplete, and blood flow through the pulmonary arteries is inadequate. Failure to synthesize enough nitric oxide (NO) is one cause.

Shortly after the baby, the placenta and the remains of the umbilical cord (the "afterbirth") are expelled.

At the time of birth, and for a few days after, the mother's breasts contain a fluid called **colostrum**. It is rich in calories and proteins, including antibodies that provide passive immunity for the newborn infant.

Three or four days after delivery, the breasts begin to secrete milk.

- Its synthesis is stimulated by the pituitary hormone **prolactin (PRL)**.
- Its release is stimulated by a rise in the level of **oxytocin** when the baby begins nursing.
- Milk also contains an **inhibitory peptide**. If the breasts are not fully emptied, the peptide accumulates and inhibits milk production. This autocrine action thus matches supply with demand.