The First Three Weeks

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Introduction

• The lecture will focus on the early development of the embryo
• We will cover the first four weeks after fertilization.
• Will start with a fertilized egg.
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<td>Remember the timing of events during the first 4 weeks of development</td>
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<td>Identify the fetal and maternal components of the placenta.</td>
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<td>Draw a concept map that follows the blastocyst and its components thru the first three weeks of development.</td>
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<td>Understand how the vertebrate body plan is formed.</td>
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As you begin your study of embryology consider the following:

**FIGURE.** Overall prevalence of major structural or genetic birth defects,* by selected maternal and infant characteristics and maternal race/ethnicity — Metropolitan Atlanta Congenital Defects Program (MACDP), 1978–2005†

*MACDP defines major structural or genetic birth defects as conditions that 1) result from a malformation, deformation, or disruption in one or more parts of the body, a chromosomal abnormality, or a known clinical syndrome; 2) are present at birth; and 3) have a serious, adverse effect on health, development, or functional ability.

† 2005 data are preliminary. Mantel-Haenszel test for trend, p = 0.19.
Week 1-3

During the first four weeks we see the formation of the:

- Blastocyst – forms during first week
- Bilaminar disc – forms during second week
  - Gastrulation - starts during the third week
- Trilaminar disc – exists during the third week

Vertebrate body plan – complete by the end of the 4th week (day 30)
• Ovulation occurs on Day 14 of the menstrual cycle which is considered day 0 of gestation.
• Fertilization occurs on Day 15 of the menstrual cycle or day 1 of gestation.
Week 1:

- Fertilization is the process where the:
  - Sperm penetrates the zona pellucida.
  - Sperm have Izumo1 on the surface which is redistributed during capacitation.
  - Juno, the Izumo1 receptor, is a folate receptor 4 (Folr4), a GPI-anchored protein on the egg, surface necessary for female fertility.
  - The sperm fuses with the egg plasma membrane.
  - For a nice video go to: [http://www.youtube.com/watch?v=BFrVmDgh4v4](http://www.youtube.com/watch?v=BFrVmDgh4v4)
Week 1:

- Fertilization is the process where the:
  - After the sperm fuses with the egg plasma membrane the egg completes the second meiotic division.
  - Juno is rapidly shed from the oocyte membrane a relatively rapid block to polyspermy.
  - The cortical reaction occurs releasing enzymes for changing the zona pellucida.
  - The zona reaction occurs so that polyspermy is prevented but this is a slower process.
  - The pronuclei of the egg and sperm unite.
  - For a nice video go to: http://www.youtube.com/watch?v=BFrVmDgh4v4
Week 1:

- When the pronuclei of the egg and sperm unite.
  - Two pronuclei appear identical.
  - DNA in pronuclei is replicated (23 chromosomes in chromatid pairs)
  - Membranes around pronuclei dissolve.
  - Now zygote is cell with 2N DNA and 46 chromosomes
  - Genetic sex determined by number of X and Y chromosomes
Week 1:

- Once the two pronuclei combine the fertilized egg is call a zygote.
- The zygote will begin a series of reduction divisions.
- During these divisions the daughter cells each become smaller.
- At the four cell stage each cell is still capable of becoming an embryo.
- By the eight cell stage the cells will begin to change and by day 3 the cells within the still intact zona pellucida are called a morula.
Week 1:

- Continuing down the uterine tube the morula undergoes the process of compaction.
  - Compaction is the process where the outer cells develop tight junction and form a seal that separates the inner cells from the outside world.
  - Once this happens the formation of Na+-K+-ATPase (Sodium) pumps on the outer cell plasma membranes moves fluid into the center of the morula.
  - This fluid forms a space within the morula called the blastocoele.
Week 1:

- There is a blastocyst cavity at day five of gestation or 19 days after the beginning of the women’s last menstrual period.
  - As the blastocyst cavity enlarges two groups of cells emerge.
    - The first are the cells that developed tight junctions and formed the periphery of the blastocyst. These are call trophoblast cells.
    - The trophoblast cells will form the fetal components of the placenta.
    - The second are the inner cells that will go on to form the embryo. These are called the inner cell mass.
• When the enlarged blastocyst emerges from the zona pellucida it is said to have hatched.
• It will soon enter the uterus and if conditions are appropriate will implant at around the end of the first week.
This slide is from the Stanford IVF clinic website listed below. It shows in vitro pictures of the different stages of the embryo from fertilization through the end of the first week.

[Slide image with stages: zygote, 2-cell, 4-cell, multi-cell, morula, blastocyst]

* inner cells of the morula form the inner cell mass; ^ outer cells of the morula form the trophectoderm

Images are courtesy of Dr. B. Behr and the Stanford University IVF clinic.

http://yaolab.stanford.edu/images/Slide7_earlymouseemb.jpg
Week 1

• The blastocyst consists of:
  - Inner Cell Mass (embryoblast)
  - Trophoblast
  - Blastocyst cavity

• As the embryo enters the uterus it consists of:
  - Inner cell mass
  - Trophoblast
  - Blastocyst cavity.
The fetal components of the placenta will come from the trophoblast cells.
The cytotrophoblast cells give rise to a second population of cells called the syncytiotrophoblast cells. Both populations invade the endometrium of the uterus. They will come in contact with maternal blood vessels around day 10 of gestation.
As the embryo implants into the endometrium, a second cavity will form the amniotic cavity. Below this the inner cell mass has become two layers of cells: epiblast layer and a hypoblast layer. It is called a bilaminar disc at this time. The blastocyst cavity then gets renamed as the primary yolk sac. A new layer of cells surrounding the yolk sac is the exocoelomic membrane.
This is an image from the National Museum of Health and Medicine. It shows the implanted embryo with the amniotic cavity, the bilaminar disc, and the primary yolk sac surrounded by cytотrophoblast and syncytiotrophoblast cells invading the endometrium of the uterus.
As the embryo continues to implant the tissue between the cytotrophoblast and the exocoelomic membrane expands. As it does, it becomes the extraembryonic mesoderm.
As the second week of gestation proceeds, lacunae or spaces appear in the extraembryonic mesoderm.
Day 11

And by day 11 this is what the embryo looks like. It is a bilaminar disc with an amniotic cavity, a yolk sac, extraembryonic mesoderm with lacunae all embedded in the endometrium with the forming cells of the placenta.
Week 2: Early Development

Cytotrophoblast
Epiblast
Hypoblast

Extraembryonic Somatopleuric mesoderm
Extraembryonic Splanchnopleuric mesoderm

Extraembryonic Coelom

Connecting stalk

Amniotic Cavity
Primary Yolk Sac

The spaces in the extraembryonic mesoderm soon coalesce to form the extraembryonic coelom. This cavity is surrounded by extraembryonic somatopleuric and splanchnopleuric mesoderm. The one exception is where the bilaminar disc is attached to the placenta which is called the connecting stalk.
At the end of the second week of gestation:

- The embryo consists of the:
  - Amniotic cavity
  - Bilaminar disc
  - Primary yolk sac

- It is connected to the placenta via the connecting stalk.

- It lies within the extraembryonic coelom or the chorionic cavity.

- The embryo is receiving maternal blood via the maternal blood vessels with are coming in contact with the cytotrophoblast and syncytiotrophoblast cells.

- The syncytiotrophoblast cells begin producing hCG human chorionic gonadotropin.
Confirmation of Pregnancy.

- Human Chorionic Gonadotropin (hCG) is produced by the syncytiotrophoblast cells.
- hCG maintains the corpus luteum for production of progesterone.
- hCG can be detected by day 14 of pregnancy or 28 days LMP.
- As soon as lacunae are formed and communicate with maternal blood, hCG is detected in the woman’s urine. Current pregnancy kits can detect pregnancy as early as day 14 of gestation.
During the third week of gestation or the 5th week LMP the embryo undergoes gastrulation. The bilaminar disc becomes a trilaminar disc. We can view this process from above the bilaminar disc.
When looking down on the bilaminar disc we see the epiblast layer (in blue). Above it is the amniotic cavity. Below is the hypoblast layer (Yellow). Below that layer is the yolk sac.

Cells of the epiblast will begin to divide in the caudal part of the embryo.
Gastrulation

- This image from the embryology website of Dr. Mark Hill is of an embryo at 17 – 19 days of gestation. You are looking down at the epiblast cells. Note in the caudal midline the cells are beginning to divide and form a line.
Gastrulation

FGF8 is expressed in the epiblast and downregulates E-cadherins. E-cadherins normally bind epiblast cells together. However during gastrulation these dividing cells will dissociate and move from the epiblast to the underlying hypoblast or to the region between the hypoblast and the epiblast.

The first region where these proliferating cells accumulate is called the primitive node. Cells continue to proliferate caudally and form the primitive streak.
FGF binds to the FGF reception on the plasma membrane and initiates a MAP kinase cascade that leads to the expression of brachyury
Gastrulation

FGF8 upregulates Brachyury (T-box gene). Brachyury is a transcription factor and is essential for mesoderm formation and formation of posterior body structures.
Gastrulation

Gastrulation is a much more complicated process and as seen here a number of genes have significant effects on the gastrulation process.
Gastrulation

However the process leads to the epiblast cells giving rise to the three germ layers: ectoderm, mesoderm and endoderm.

If the embryo is sectioned and view from the caudal region as depicted here the image in the next slide is seen.
Gastrulation

Seen here the epiblast cells are giving rise to cells that will become notochord or mesoderm (red). Another group of cells will replace the hypoblast cells and become the endoderm (yellow). Most of the hypoblast cells will migrate and line the primary yolk sac.
In this image, the pink arrows depict the movement of mesoderm cells cephalically and laterally (pink). The notochord cells (purple) move in a cephalic direction and come to lie in the midline between the newly formed endoderm (yellow) and the renamed ectoderm (blue).
So we now have a trilaminar disc with the remaining epiblast cells called the ectoderm, the middle layer called the mesoderm and notochord (purple cells in the midline), and the ventral layer called the endoderm.
Four signalling pathways are involved in mesoderm formation:
1. Nodal (including Activin and Vg1)
2. FGF (Fibroblast growth factor)
3. Wnt
4. BMP (Bone morphogenetic protein)
The four main signaling pathways interact in different ways to regulate the formation of the head, trunk and tail mesoderm.
Body Axis Formation

Nodal, Lefty and snail all play a role in left/right symmetry.

For example the heart is the first asymmetrical organ to develop.
The liver ends up on the right side of the body.
The stomach is on the left.
Gastrulation

If viewed from the midsagittal plane the development of the notochord can be examined.
Gastrulation

The cells forming the notochord migrate in the midline in a cephalic direction.

As they lie in between the ectoderm and mesoderm they form a tube called the notochordal process.

The notochordal process will then fuse with the endoderm. Thus forming the notochordal plate.

At this time the amniotic cavity and the primary yolk sac are in communication.

Then the notochordal cells will round up again and form the notochord proper.
Gastrulation

Making a coronal section in the plane of the green line and looking from the caudal end of the embryo you would see the image in the next slide.
And this is what the human embryo looks like at 20 days of gestation after gastrulation has taken place. You are looking down at the ectoderm and can see through it at some of the mesoderm.
After three weeks

- The trilaminar disc lies between the amniotic cavity and the yolk sac.
- The embryo is connected to the placenta via the connecting stalk.
- The embryo lies within the chorionic cavity.
- During the next week it will undergo lateral body folding and head and tail folding to develop the vertebrate body plan.