Insights into MAnaging Growth for Endocrine Nurses

Normal sex development

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Disclosures

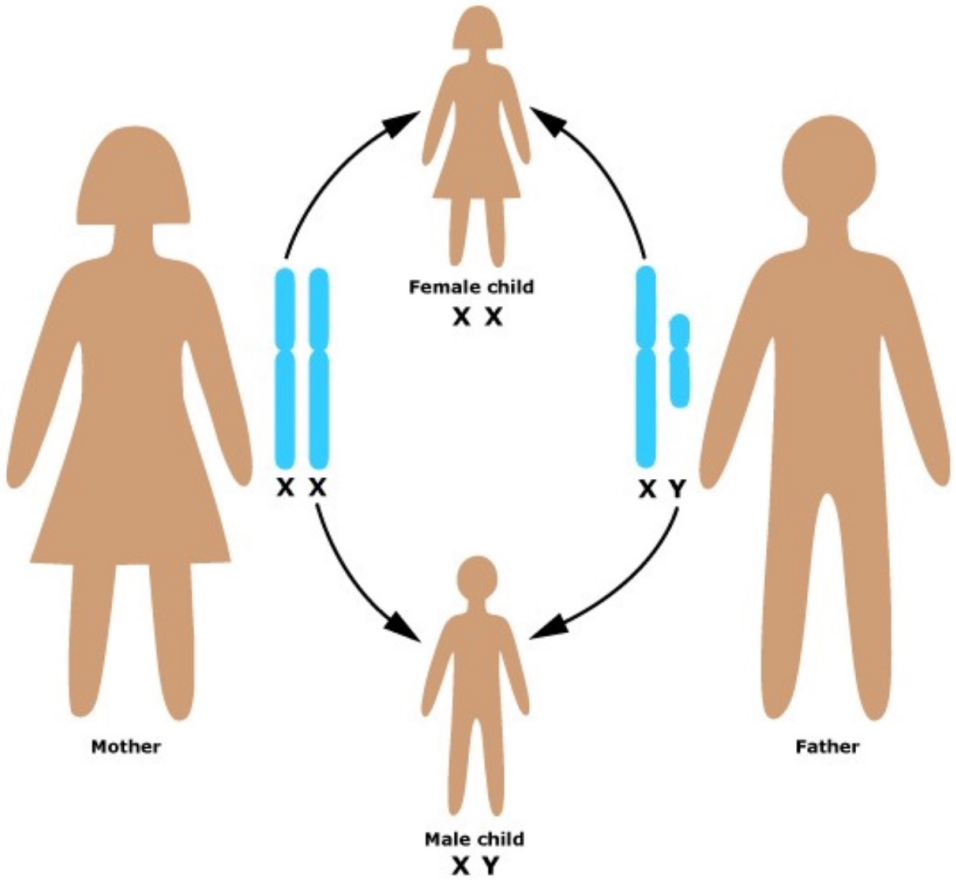
- Honoraria
  - Novo Nordisk
  - Ipsen Ltd
  - Sandoz Ltd

Introduction

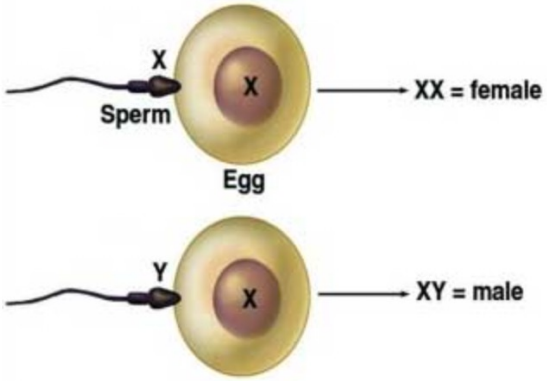
- Sex determination
- Embryology
- Genital ducts
  - Masculinisation
  - Feminisation
- Gonads
  - The Testis
  - The Ovary
- Hormones
- Patient-focused description
  - ‘Story of Sex Development’

www.study.com

Determination of Sex



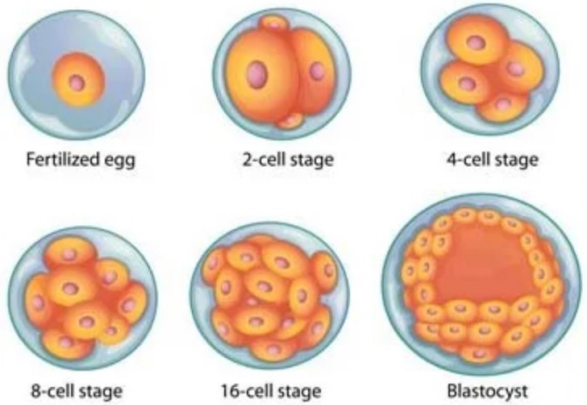
Graphic 76396



www.whhealth.weebly.com

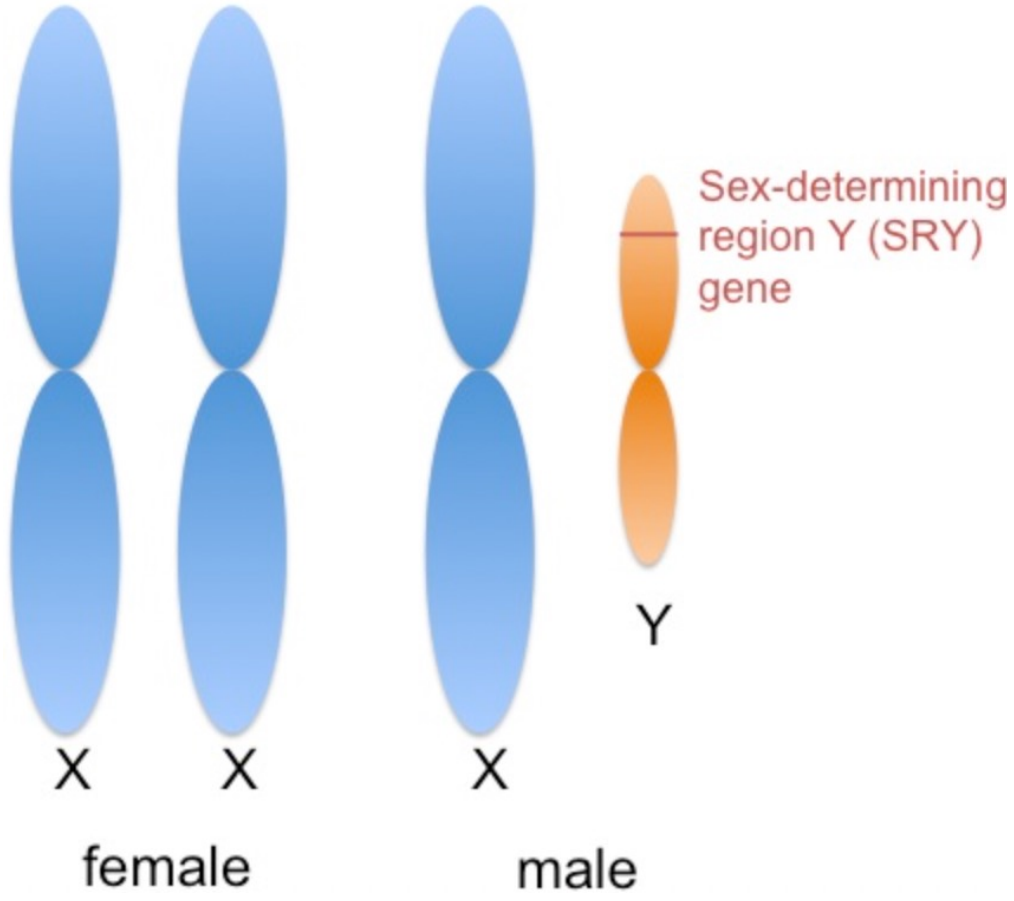
- XX – Female
- XY – Male
- Sex chromosome division
  - Blastocyst

(Hiort, 2017)



www.microbenotes.com

Determination of Sex – the Y chromosome



https://amasianv.files.wordpress.com/2012/08/xx-male1.jpeg

- SRY gene
- Signals sex-neutral tissue to develop into a pair of testes
- If SRY gene is missing or does not work

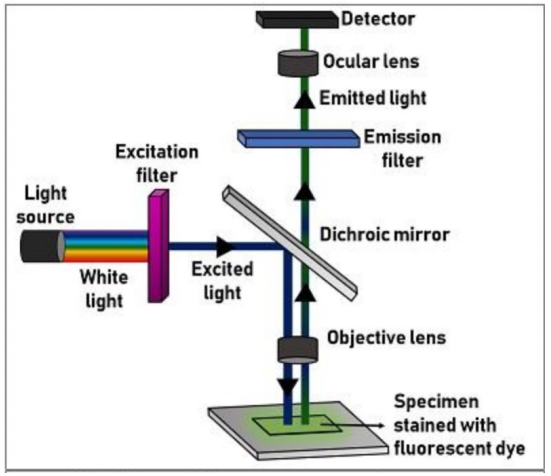
Sekido & Lovell-Badge, 2008

Wisniewski et al, 2012

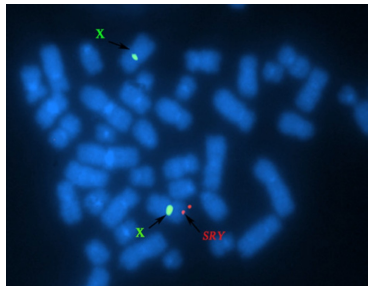
?

SRY gene location

- FISH
  - **F**luorescence **i**n **s**itu **h**ybridization
  - Cytogenetic technique
  - Can detect genetic abnormalities
  - Sample viewed under Fluorescence Microscopy



Bishop, 2010



www.biologyreader.com

North East Thames Regional Genetics Service

Full Karyotype

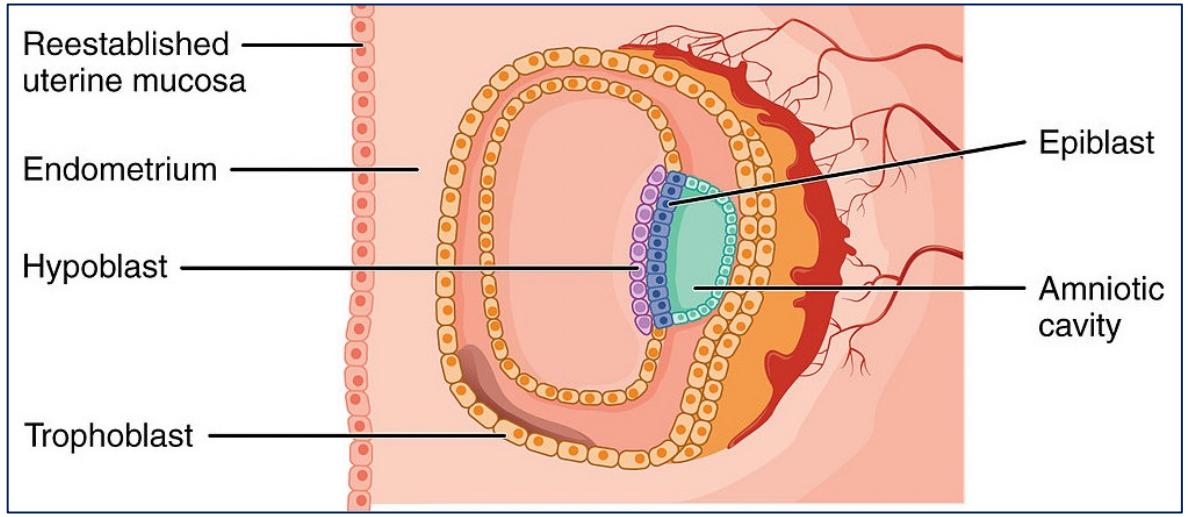
- Blood cultures are grown and harvested to yield metaphase cells which are analysed using light microscopy.

? Possible sex chromosome abnormality

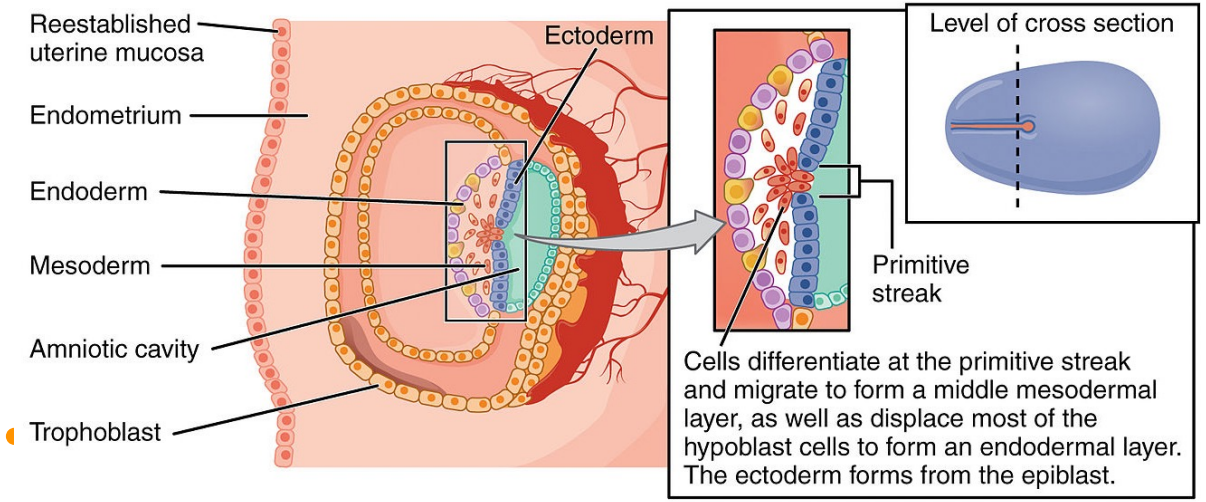
- A targeted 30 cell score for the sex chromosomes is performed
  - Not a full karyotype

Embryology – first 2 weeks

- Blastocyst
  - Implantation

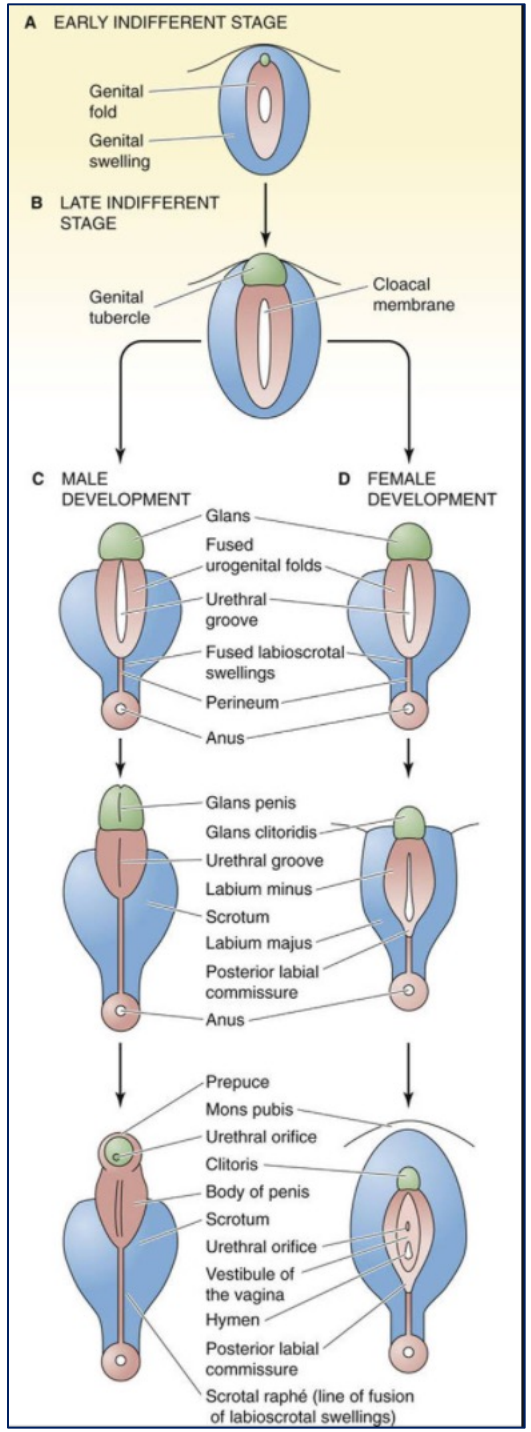


- Gastrulation
  - Day 14



- Ectoderm
- Mesoderm
- Endoderm

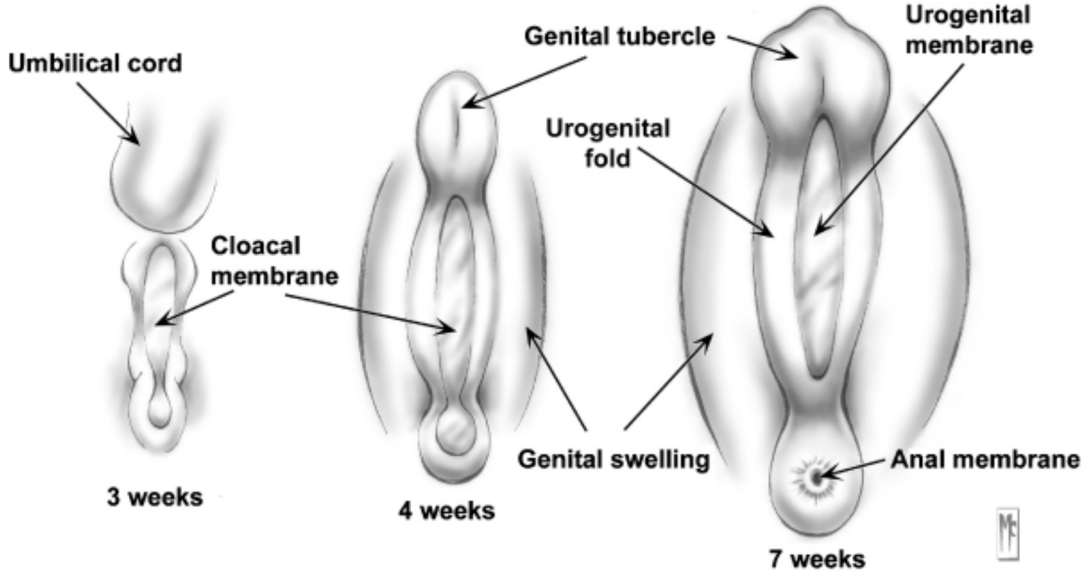
Webster & DeWreede, 2016
www.teachmeanatomy.info



Embryology – 3 – 6 weeks

- Development of the external genitalia

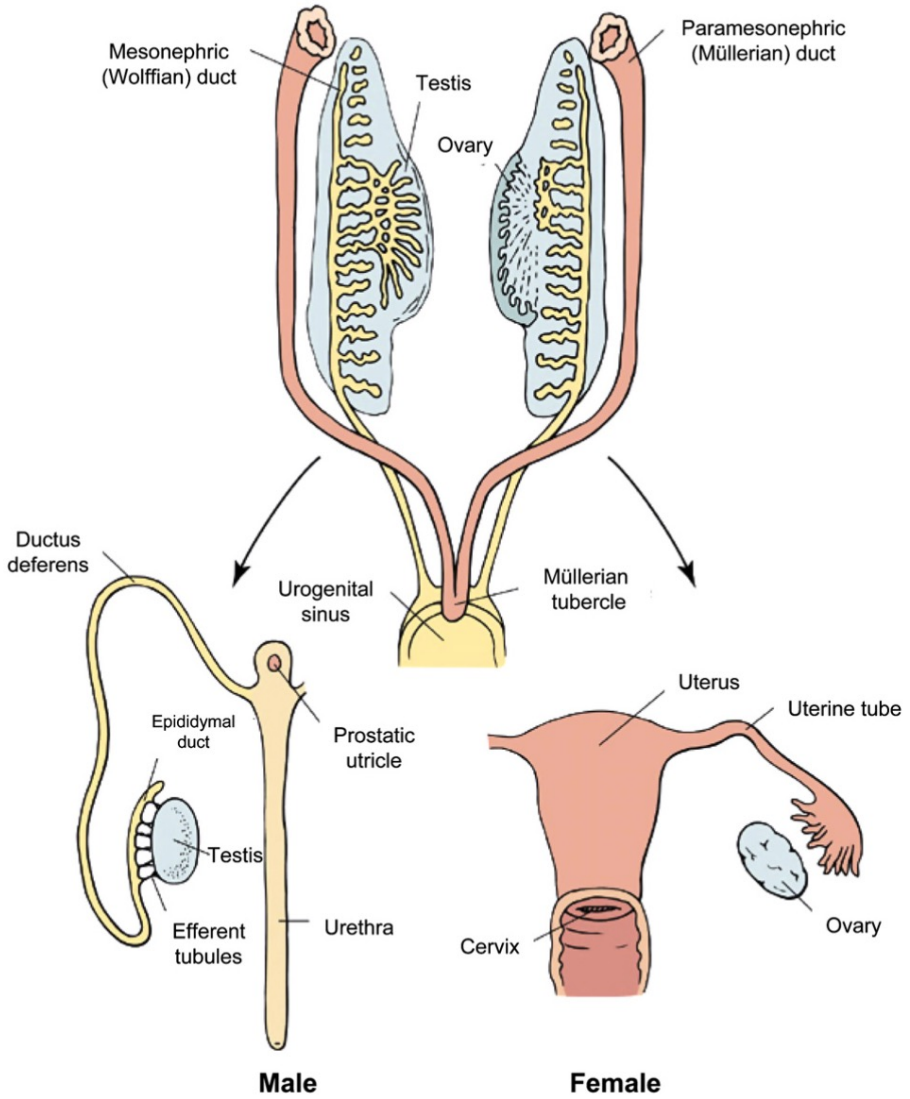
- Cloacal membrane



Yamada, 2003

www.doctorlib.info

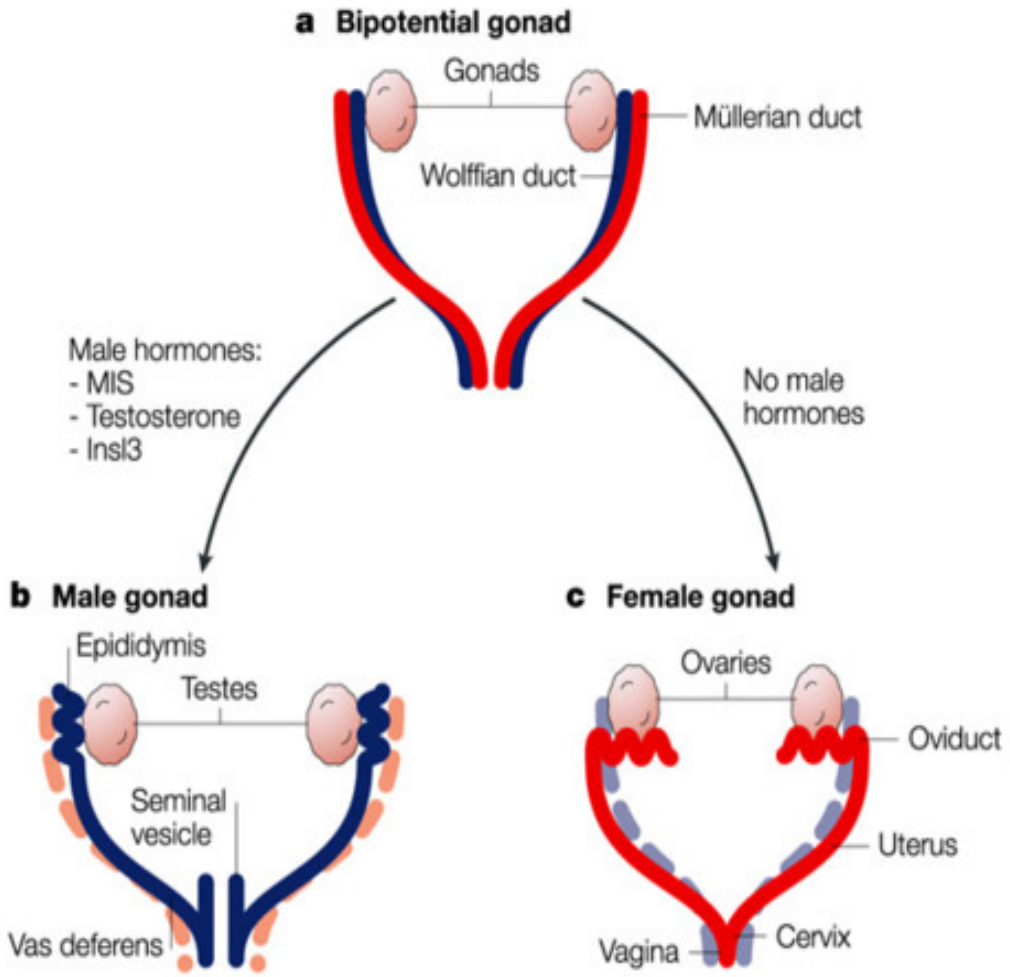
Embryology – 6 – 7 weeks



- Mullerian duct **FEMALE**
  - Paramesonephric duct
- Mesonephric duct **MALE**
  - Wolffian duct

Biason-Lauber, 2009
Hutson, 2012

Genitalia development – 7-8 weeks



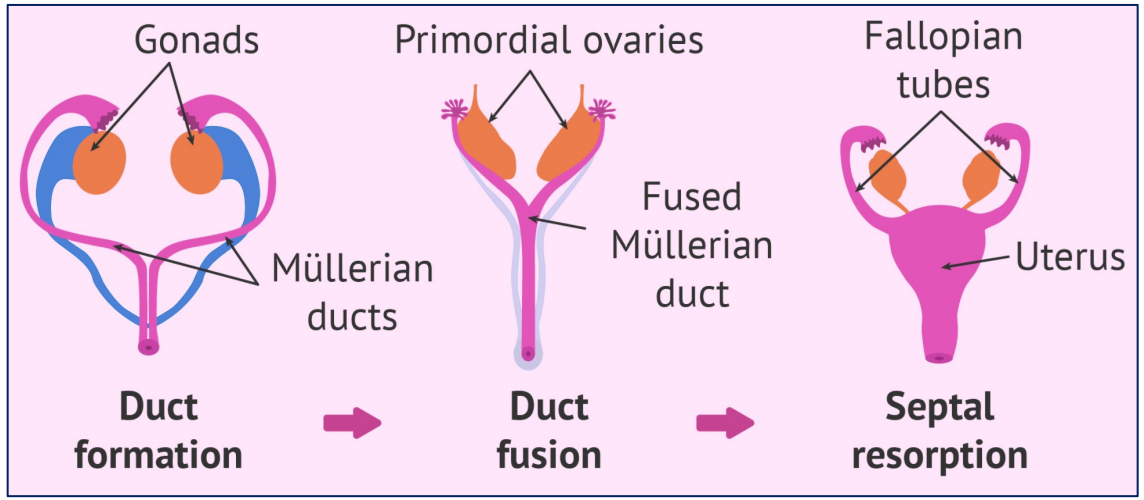
- **7-8 weeks**
  - Presence of XY chromosome
    - Triggers activation of SRY gene
    - Initiates development of a testis
    - Primary sex chords develop into Sertoli cells
      - Anti-Mullerian hormone (AMH)
      - Leads to regression of the Mullerian duct
    - Leydig cells produce testosterone
      - Stimulate Wolffian duct to form epididymis, vas deferens and seminal vesicles

Davies, 2019

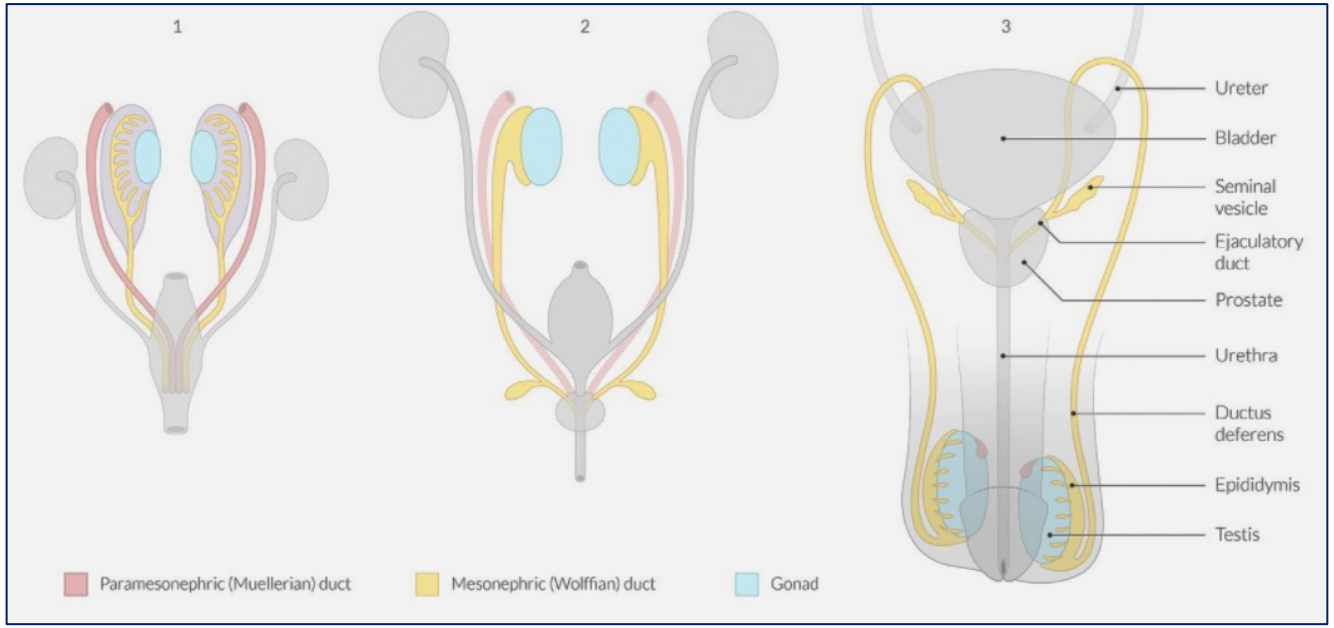
Sexual differentiation

- Mullerian Ducts
  - Initially present in both sexes
  - Regress under the influence of AMH
- Wolffian Ducts
  - Regress in the female

www. https://www.invitra.com/en/uterine-malformations/uterus/

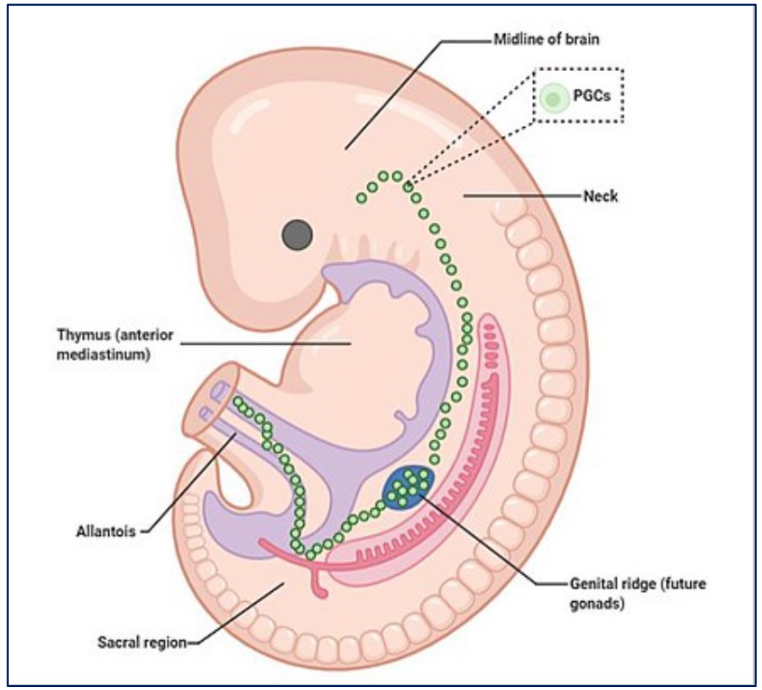


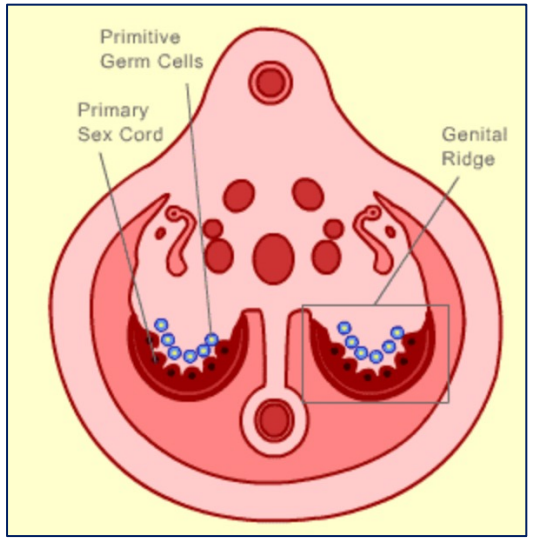
www. https://www.amboss.com/us/knowledge/Development_of_the_reproductive_system



Gonadal development

- Gonads
  - Intermediate mesoderm
  - Mesodermal epithelium
  - Germ cells
- Primordial germ cells (PGC)
  - Precursors for gametes
  - Migrate from the embryo's yolk sac to the genital ridge





- Here, they are incorporated into the primary sex cords

- Fingerlike projections that have formed over the previous week

https://en.wikipedia.org/wiki/Primordial_germ_cell_migration

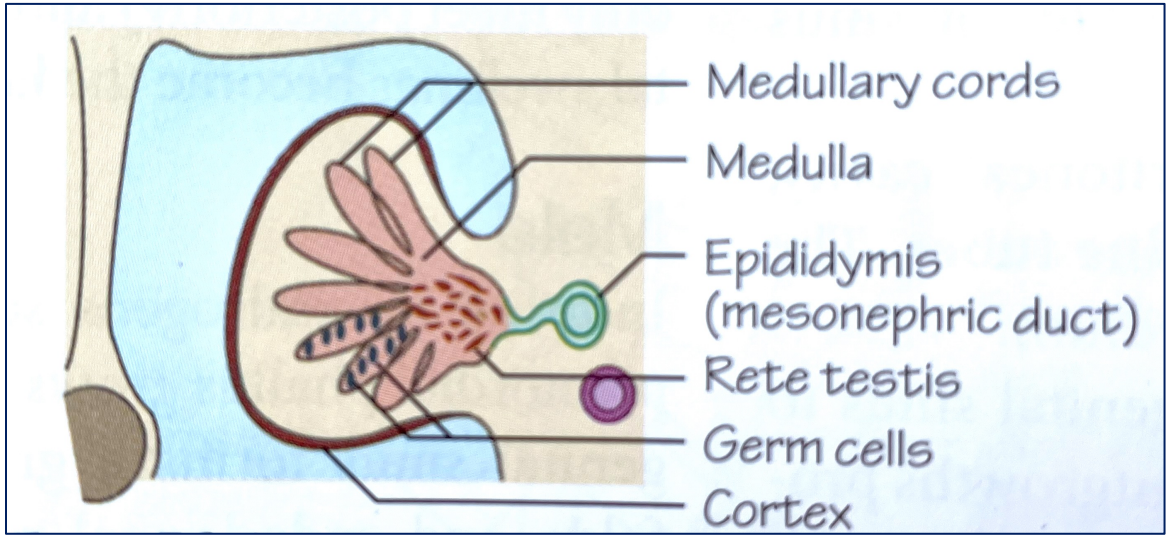
https://*www.jaypeedigital.com/eReader/chapter/9789386261205/ch1#*

The Testis

- Testis development
  - SRY gene
- After arrival of PGC
  - Sex determination occurs

(Cool & Capel, 2009)

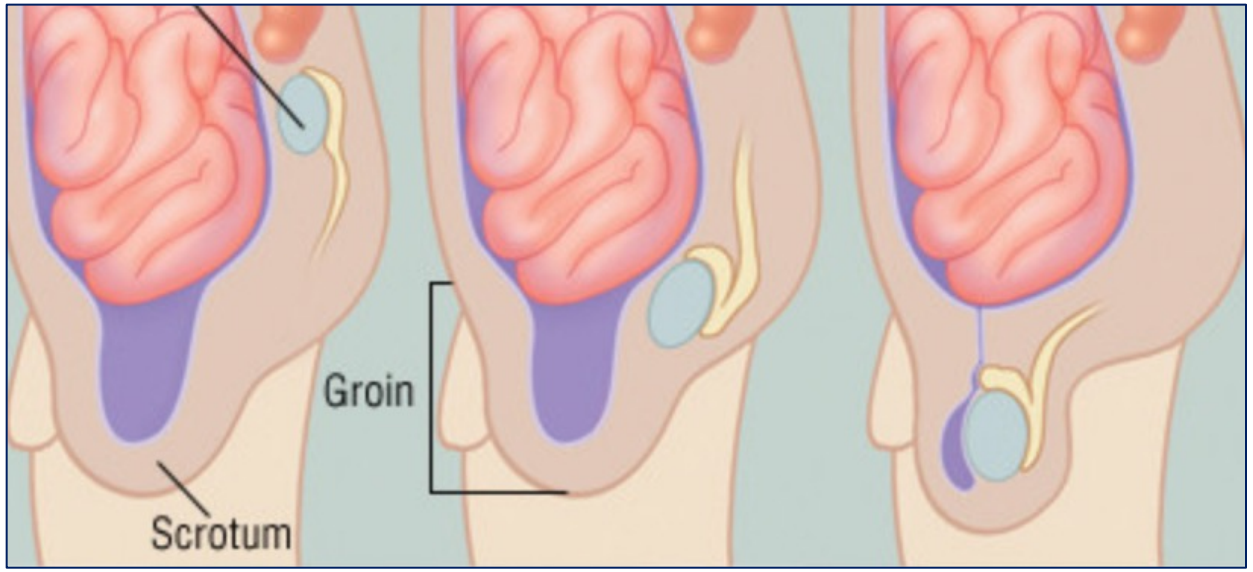
- SRY
  - Interacts with DNA



- Leydig cell development
- Rete Testis
- Seminiferous tubules

Webster & De Wreede, 2016

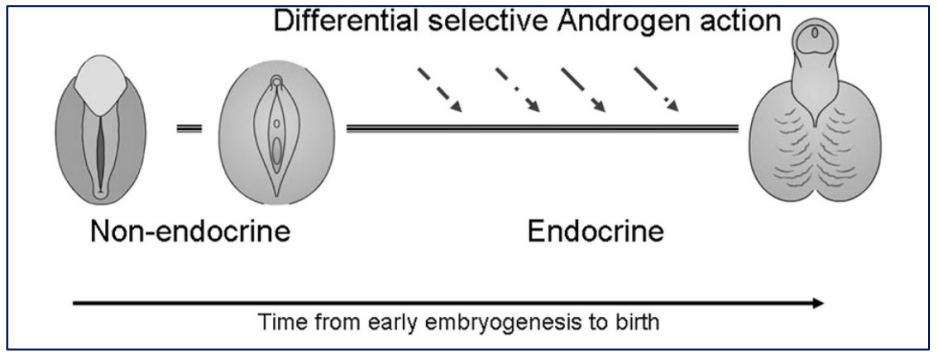
The Testis



https://www.health.harvard.edu/a_to_z/undescended-testicle-a-to-z

- Androgens
- AMH
  - Androgen insensitivity syndrome

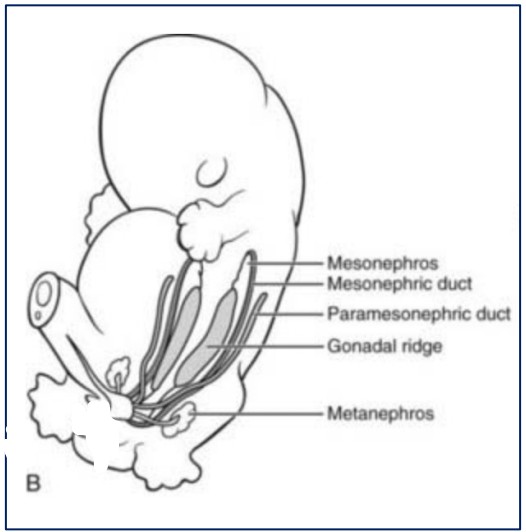
Makela et al, 2019



Hiort, 2013

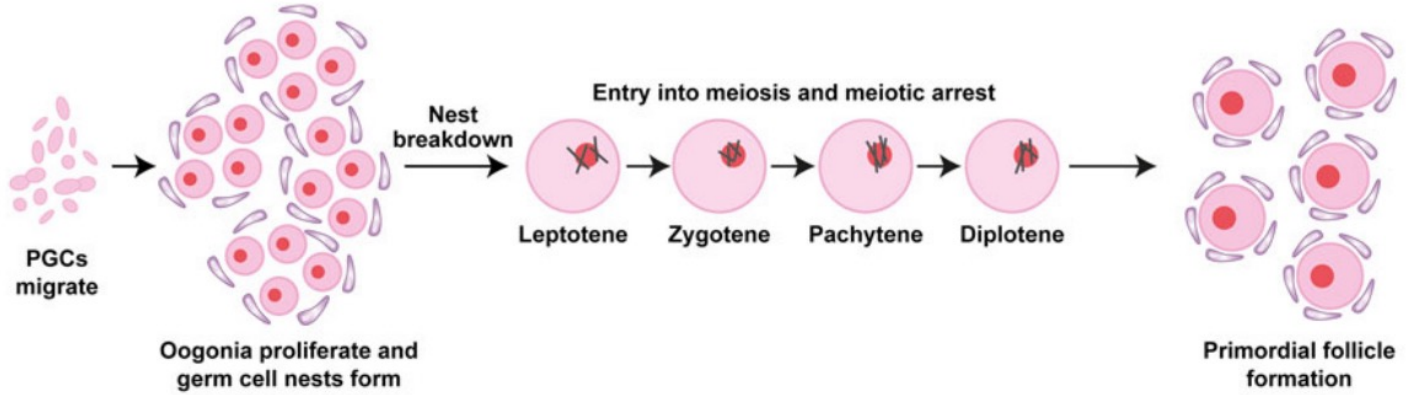
The Ovary

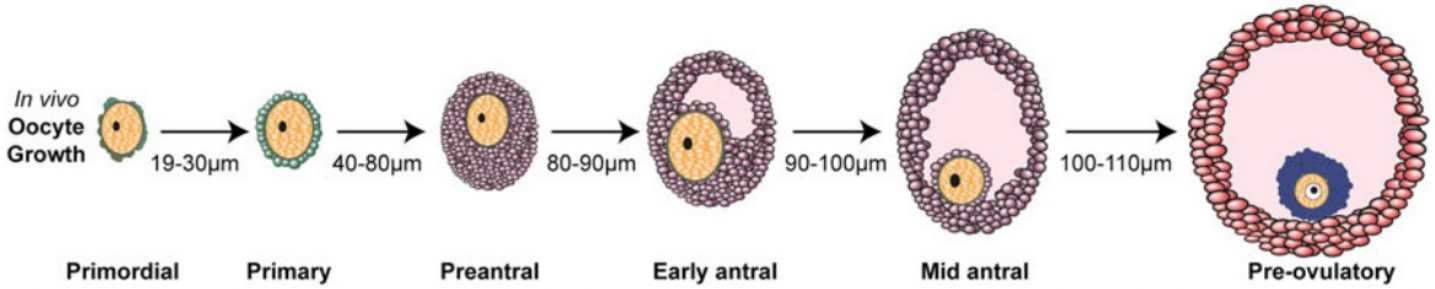
- Genetic influence
  - WTN4 *(Vainio et al, 1999)*
- Week 6 of gonadal development
  - *https://oncohemakey.com/genetic-bas gonadal-and-genital-development/*



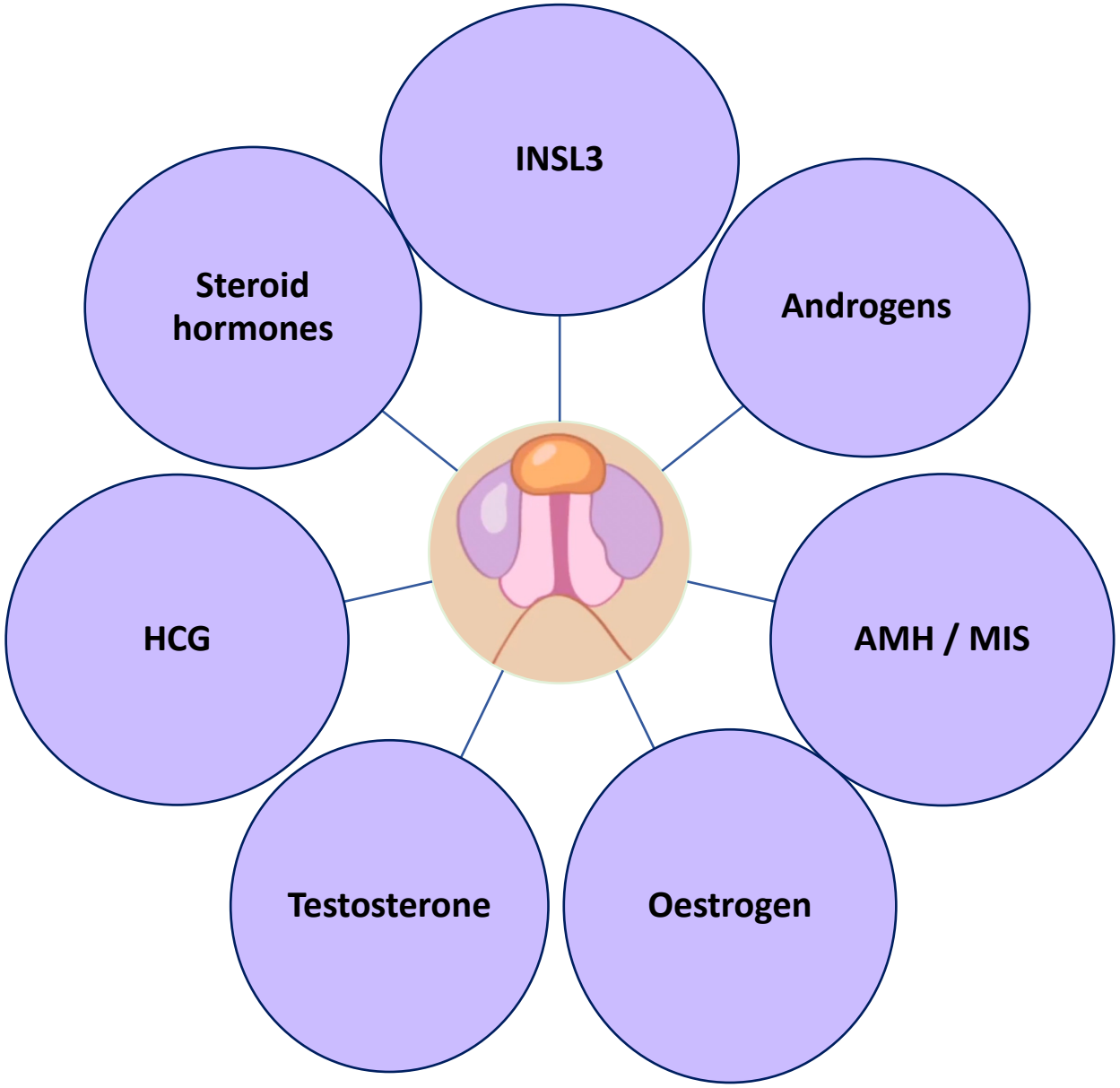
- Oocyte maturation

Telfer & Anderson 2019



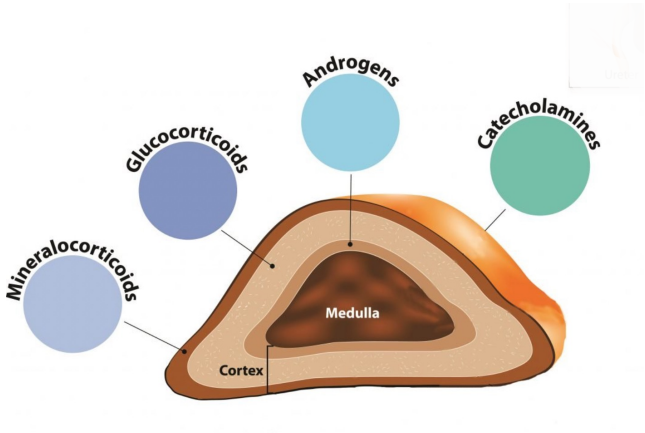


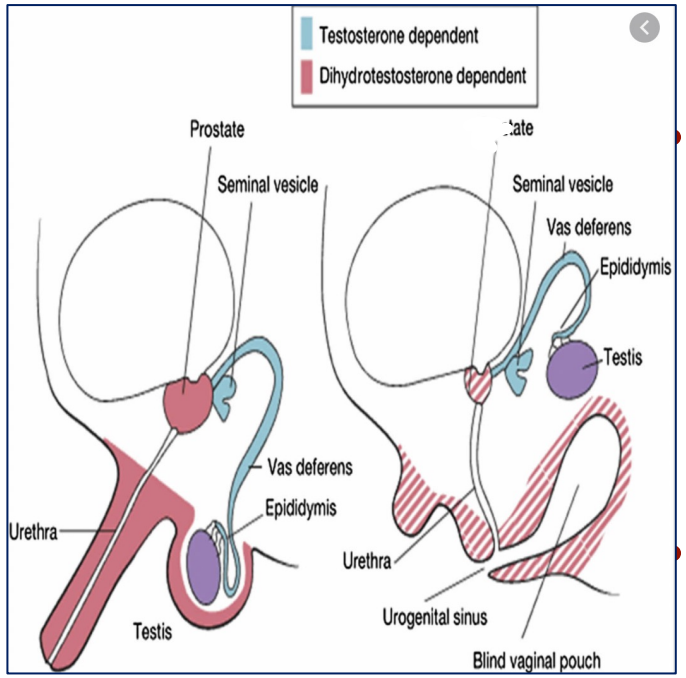
Hormones


INSL3
Steroid hormones
Androgens
HCG
AMH / MIS
Testosterone
Oestrogen

Hormones overview

- DHT
  - Dihydrotestosterone
- Androgens



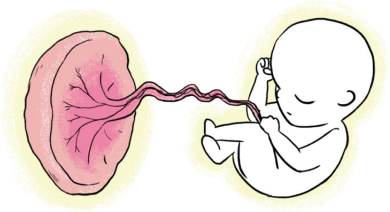


Zhu & McGinley, 2009

- AMH
  - Anti-Mullerian Hormone
  - Produced by Sertoli cells
  - Secreted into Wolffian ducts
  - Secreted into Mullerian ducts
    - Trigger regression in the male
- INSL3
  - INSulin Like Hormone
  - Produced by Sertoli cells
  - Stimulates growth of genito-inguinal ligament

https://www.hormones-australia.org.au/the-endocrine-system/adrenal_gland/

- Testosterone
  - Steroid formed from cholesterol in the Leydig cells

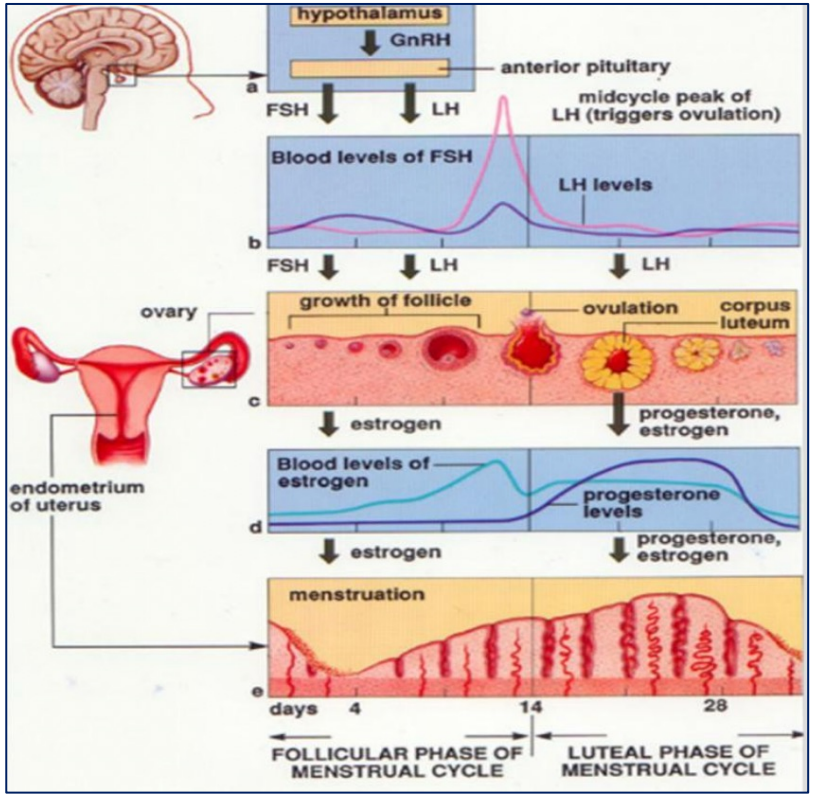


Hormones overview

- https://cradlewise.com/blog/placenta-your-babys-first-organ/

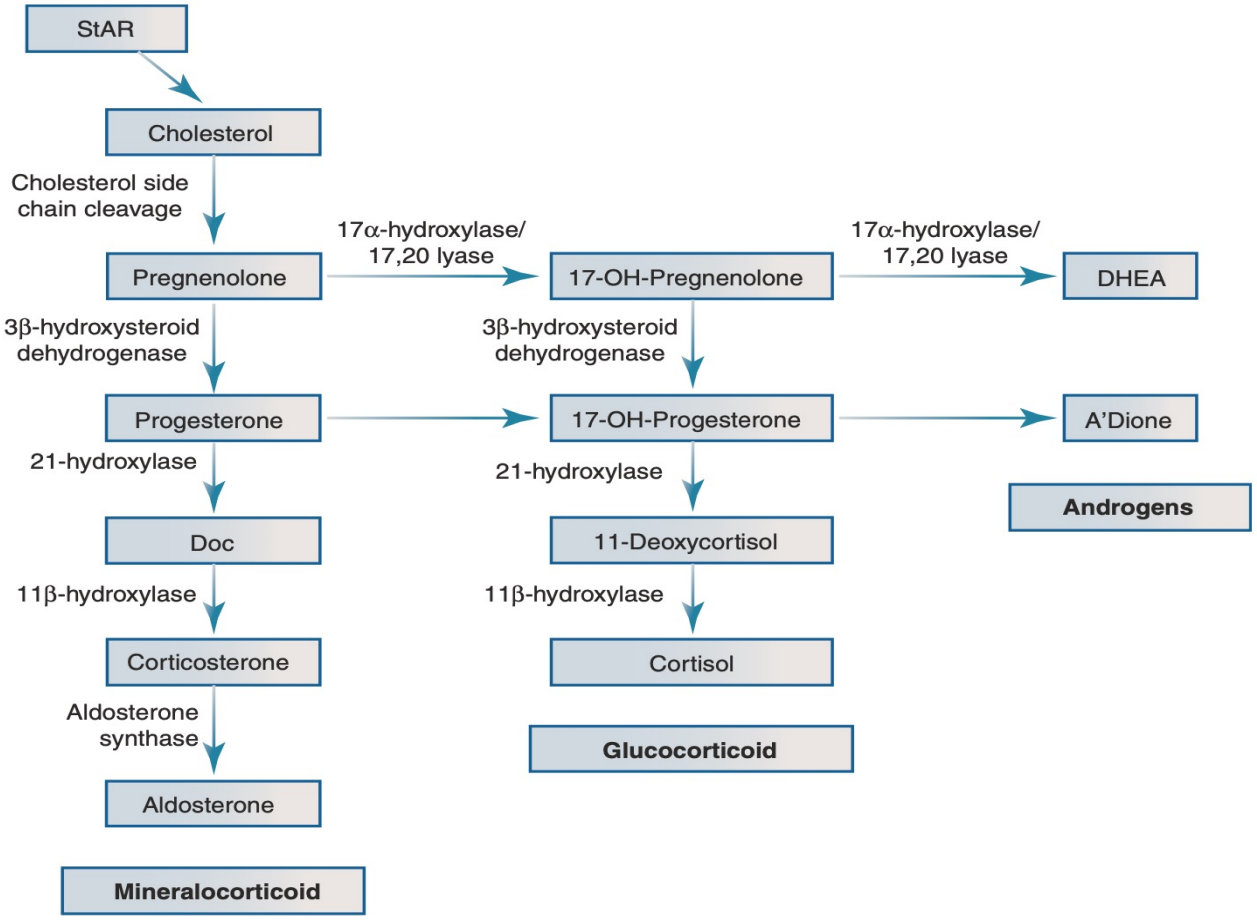
- HCG
  - Human Chorionic Gonadotrophin
- Serum levels of foetal testosterone mirror HCG, suggesting that the placenta has an important role in the early years of male sexual development
- Key masculinising effects during second half of gestation
  - Growth of penis and scrotum, and testicular descent
    - Babies with congenital hypopituitarism and anencephaly have micropenis, hypoplastic scrotum and cryptorchidism

- Oestrogen
  - Ovaries
  - Placenta



https://karenchantek.wordpress.com/2013/10/02/period/

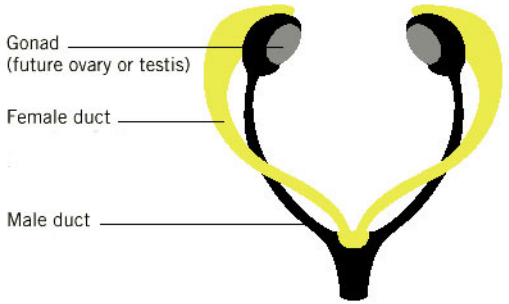
Adrenal steroid pathway

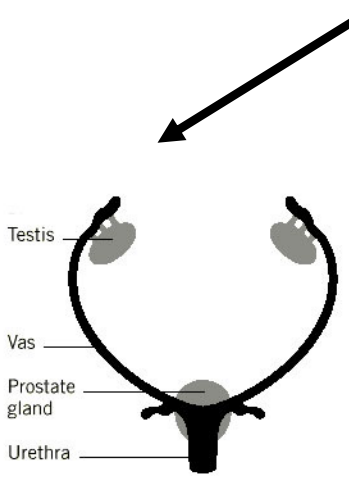


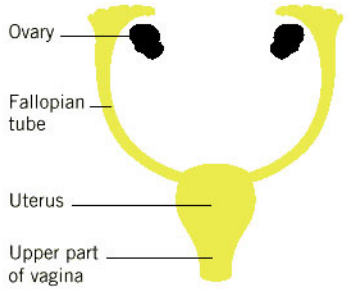
Yeoh, 2019; Turcu & Auchus, Endocrinol Metab Clin North Am, 2015

Formation of internal structures

https://iheartguts.com/







- Foetal ovaries
  - Make small amounts of testosterone and AMH
- Foetal testes
  - Make lots of both hormones
  - The presence or absence of these hormones influences the development of the internal sex ducts:
- Mullerian ducts
  - Found in boy and girl foetuses, but disappear in boys when the testes make AMH (Mullerian Inhibiting Hormone)
  - Forerunners of the uterus, cervix, fallopian tubes and upper portion of the vagina
- Wolffian ducts
  - Found in all foetuses but disappear in girls as they have no testes to produce testosterone
  - Forerunners of vas deferens, epididymides, prostate gland and seminal vesicles

https://www.ucl.ac.uk/~ucbhhks/BIOL2010/b250-99/mammalsex08.html

Story of Sex Development

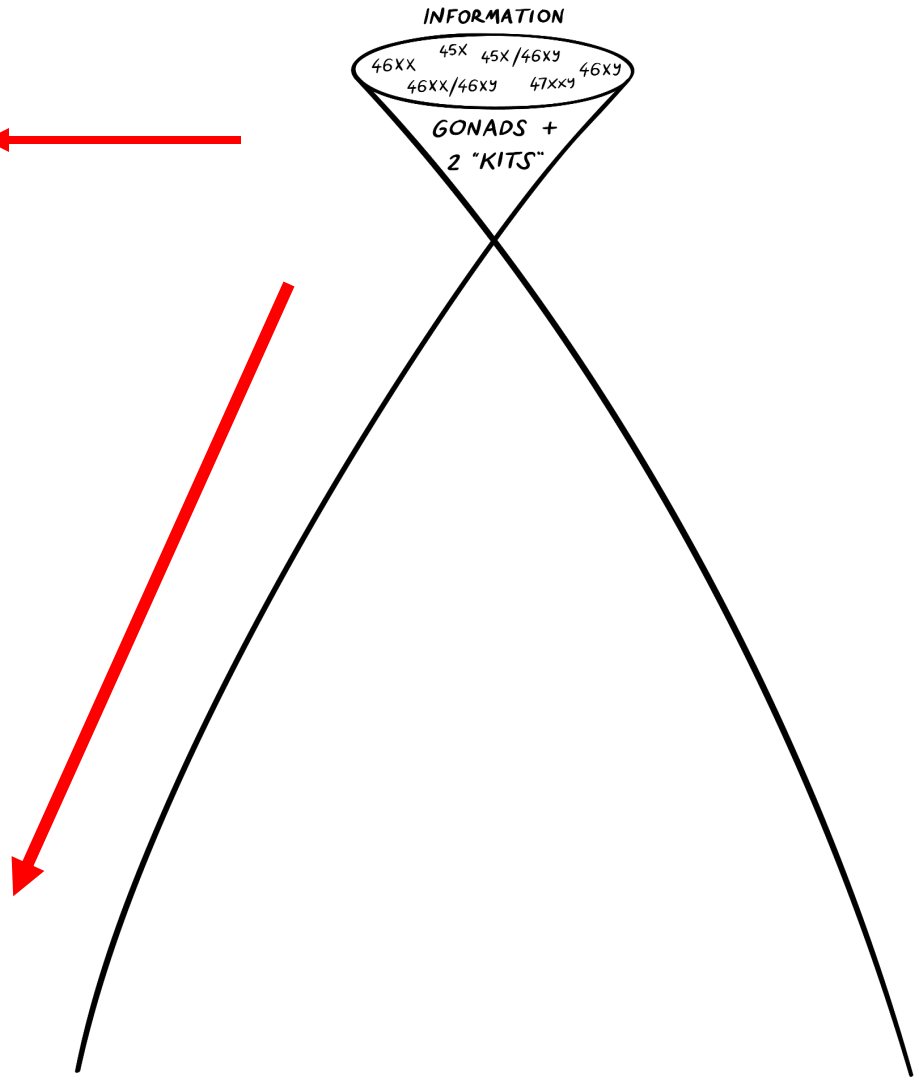
dsdfamilies

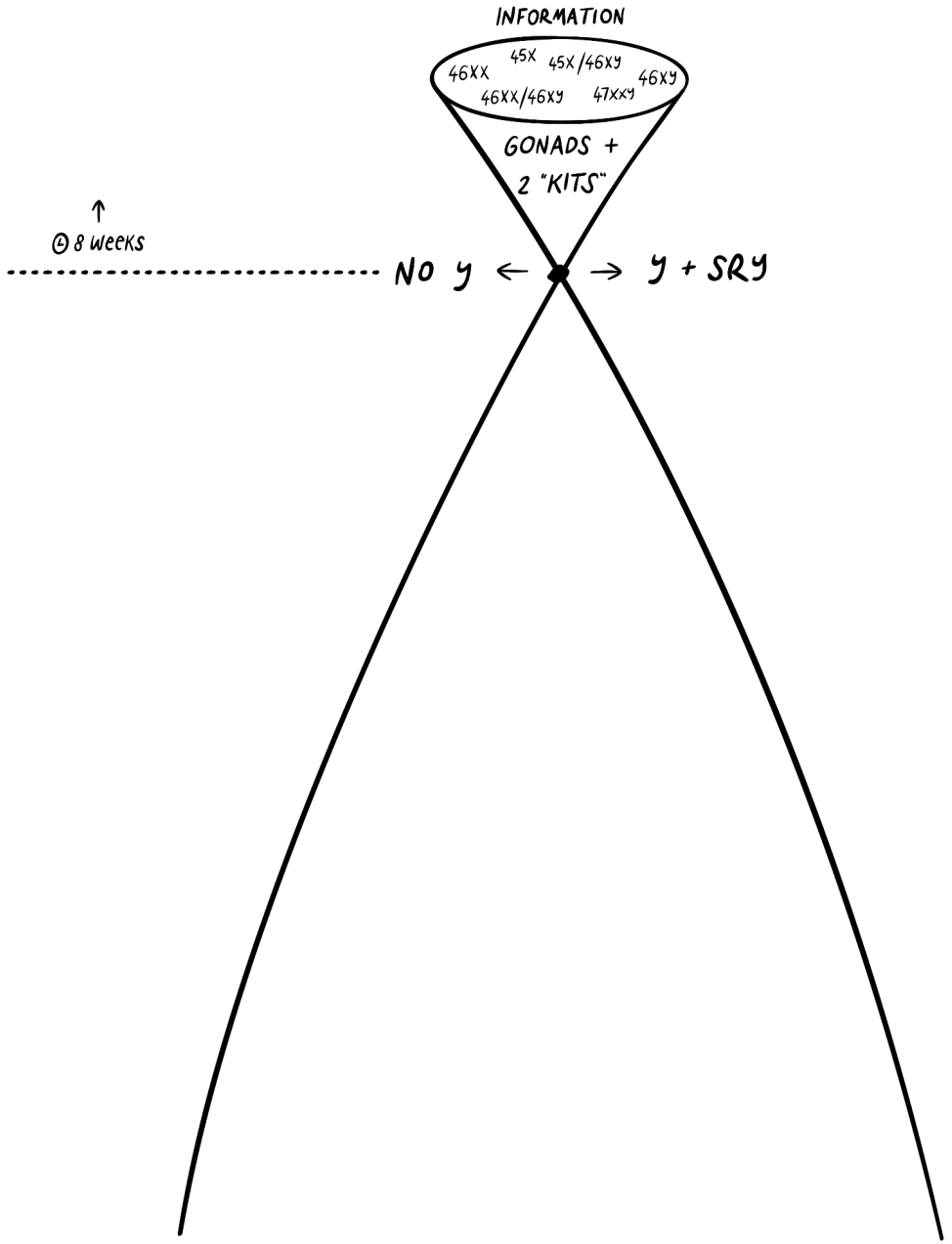
www.dsdfamilies.org

We start at the beginning…

Chromosomes we get from our mum and dad carry genetic information.
We are most familiar with 46,XX and 46,XY but other combinations also possible, eg:
-45,X (Turner syndrome)
-47,XXY (Klinefelter's)
-45,X/46,XY (Mixed gonadal dysgenesis)

Up to 8 weeks of pregnancy, we all develop in a similar way:
-with gonads that can become testes or ovaries
-with two sets of 'kit': the typical female reproductive organs kit and the typical male reproductive organs kit.

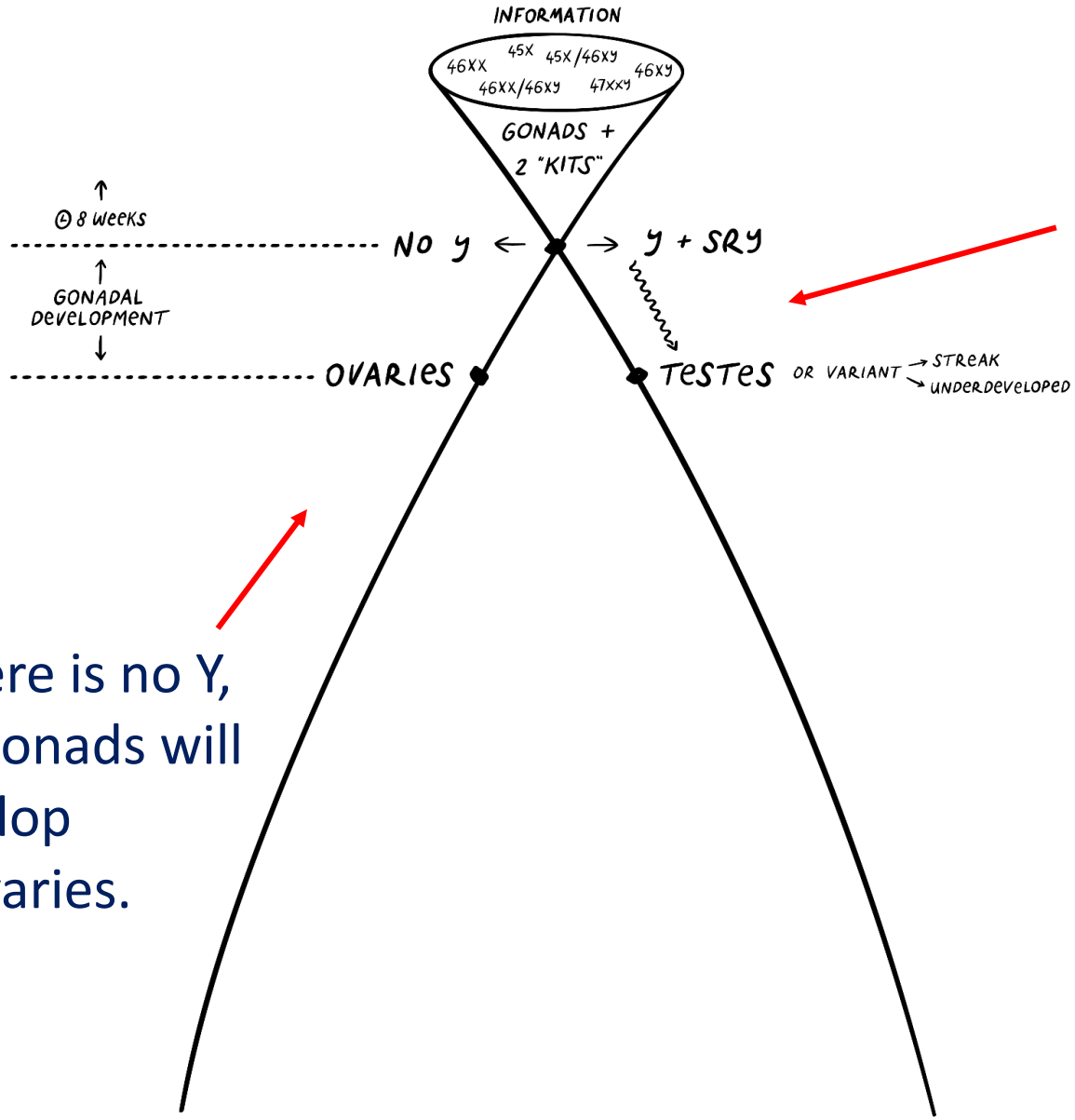




At 8 weeks of pregnancy, the process of ‘gonadal development’ begins.

Whether the gonads develop as ovaries or testes will depend on whether baby has a Y chromosome

(because there’s a gene on the Y called the SRY gene that ‘instructs’ the gonads to develop like testes)



If there is no Y, the gonads will develop as ovaries.

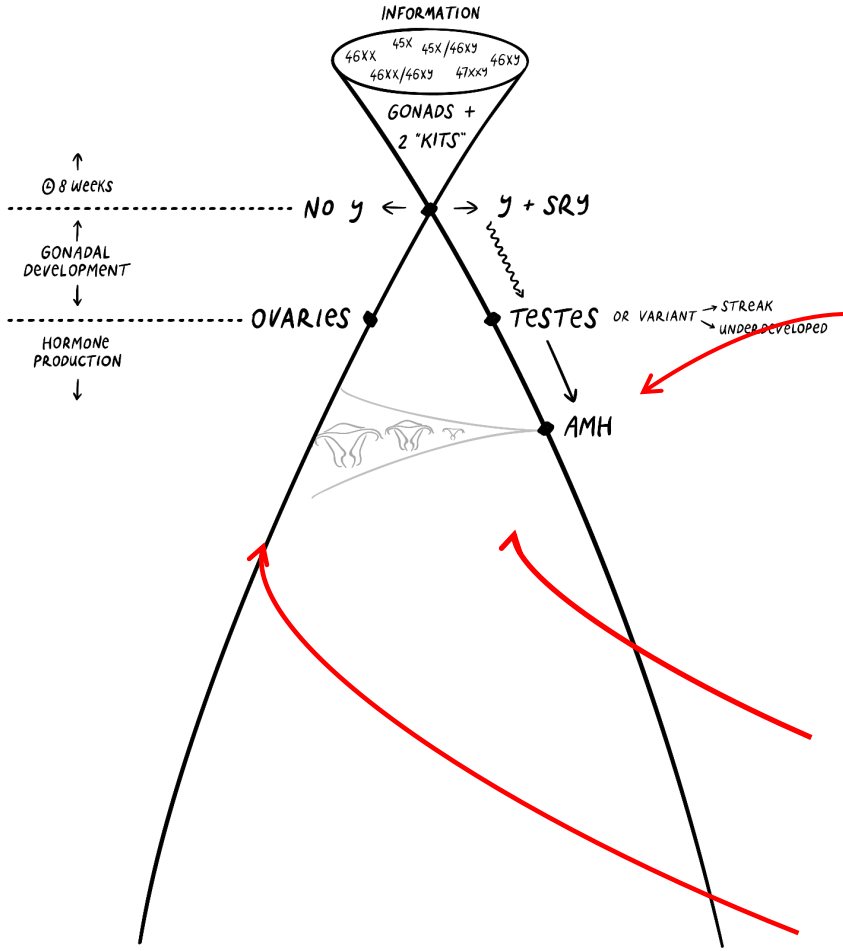
If there is a Y and a SRY gene then the gonads begin to develop as testes.

Lots can happen during this process.

Sometimes testes don't develop at all (streak).
And sometimes - for a huge variety of reasons - they are underdeveloped.

This will affect the amount of hormones they produce further down the line.

Following the process of gonadal development, let's look at the next steps: hormone production



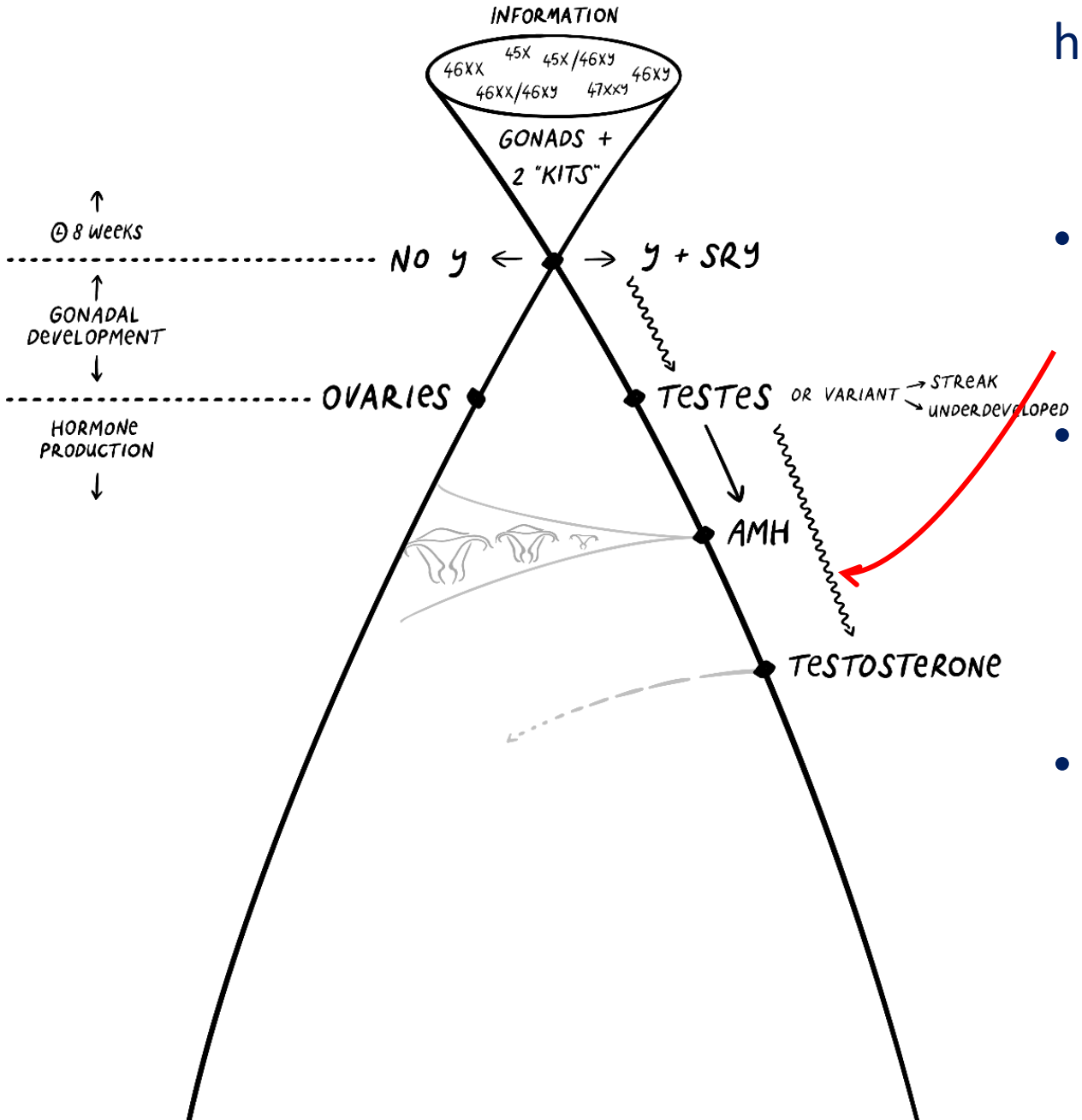
The testes produce a first hormone called AMH which seeks to 'get rid' of the female kit.

When there are typical quantities of the hormone AMH, the female reproductive structures will disappear.

The ovaries don't produce any hormones at this stage, and the typical female reproductive kit simply undergoes natural growth.

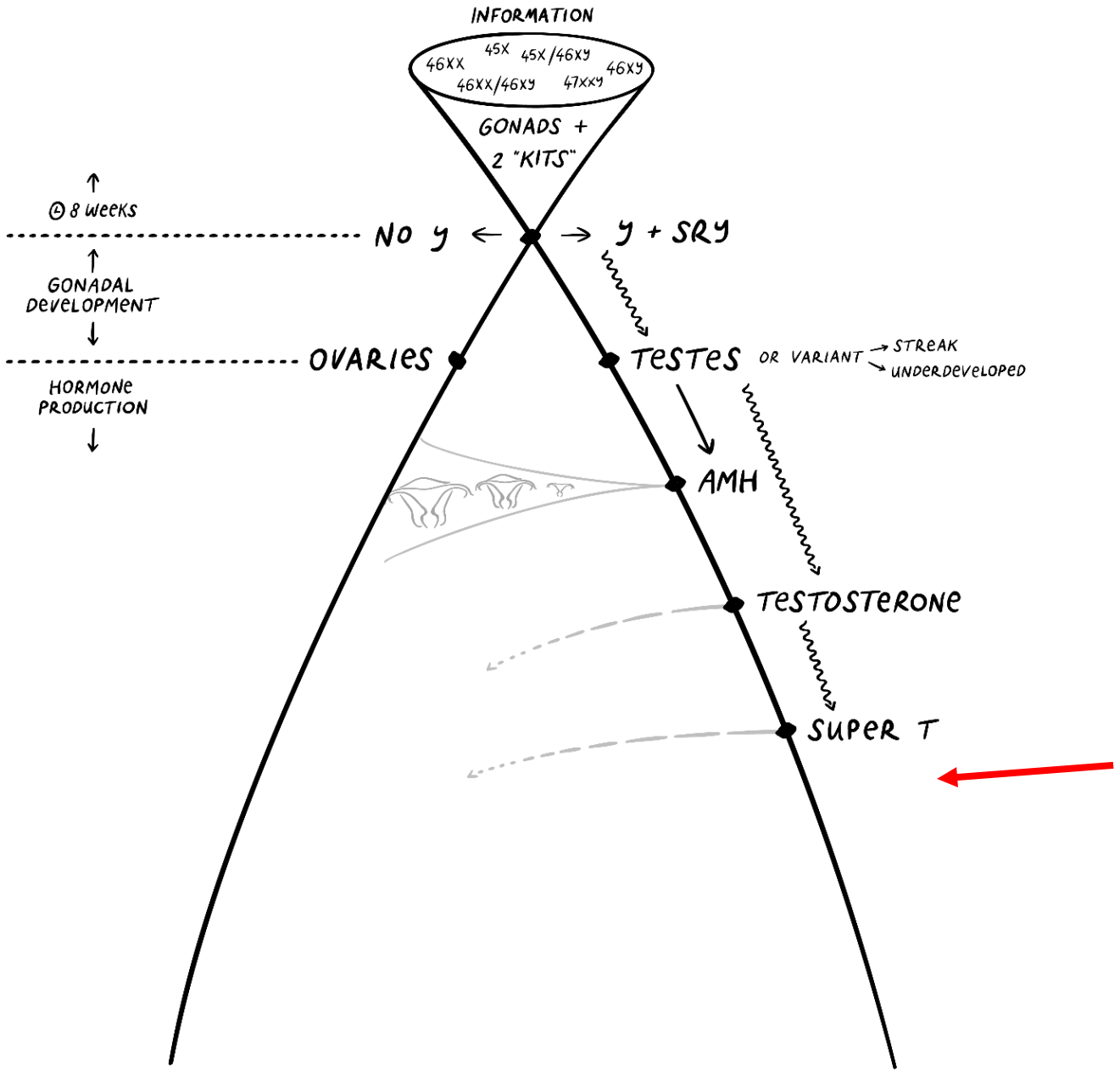
If testes are underdeveloped, there will be less AMH and we may find uterine-like structures or remnants.

If testes don't develop (just streak/ tissue), there will be no AMH and the typical female kit will simply grow.



The testes also produce another hormone called Testosterone (T).

- Usually, the testes just produce T.
- Sometimes, during the process of making T, something happens involving 'enzymes' and no or little T is produced
- And, sometimes, if the testes are underdeveloped, there will be less production of T.



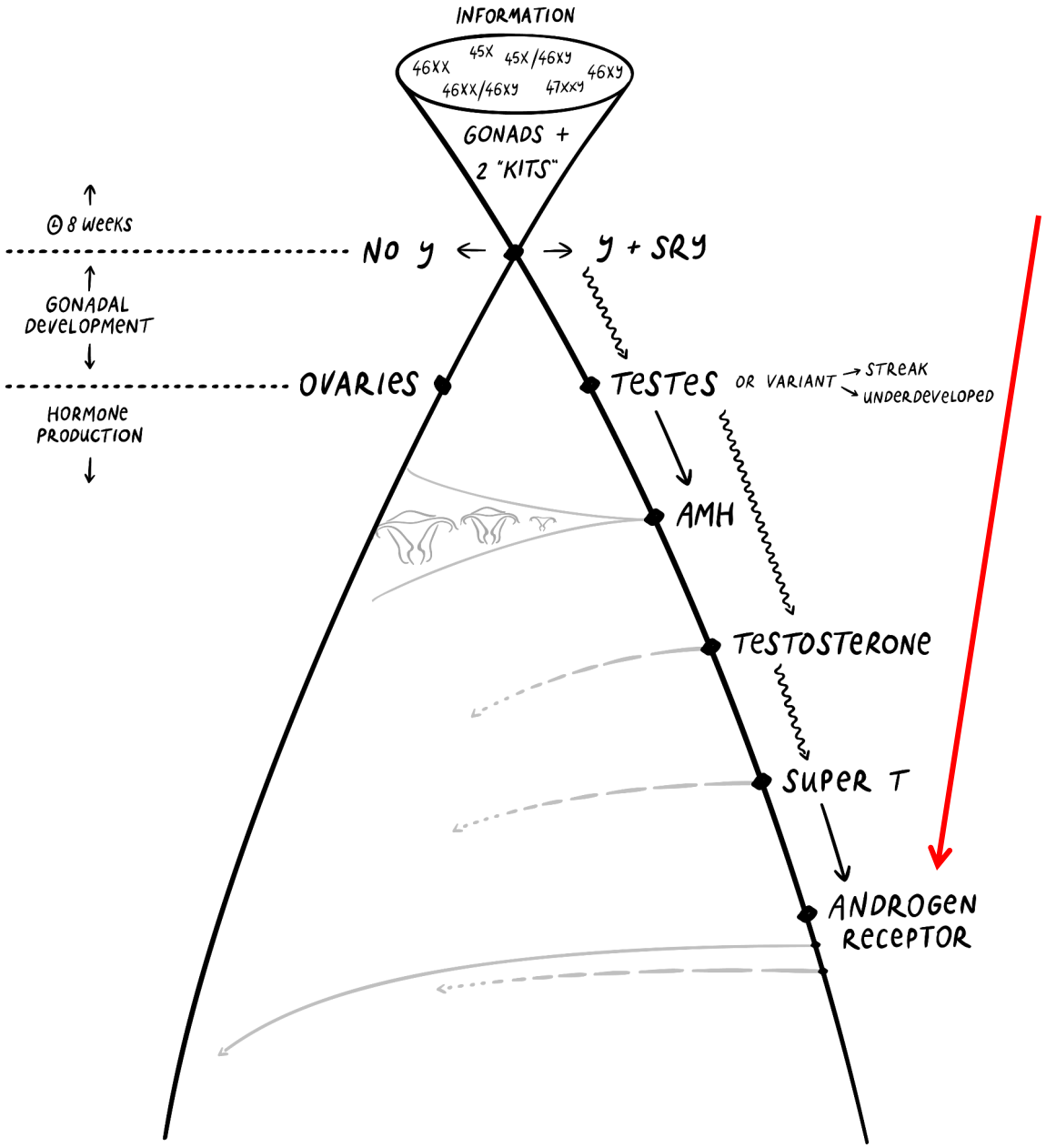
All genitals start out from similar ‘tissue’.

For genitals to change and grow into a penis and scrotum, we need a special hormone called ‘DiHydroTestosterone’ or SuperT.

Usually, T just gets converted (changed) into SuperT.

Sometimes, something happens to that conversion involving enzymes and no SuperT gets made

Other times, because testes are underdeveloped, there will be less SuperT than usual.



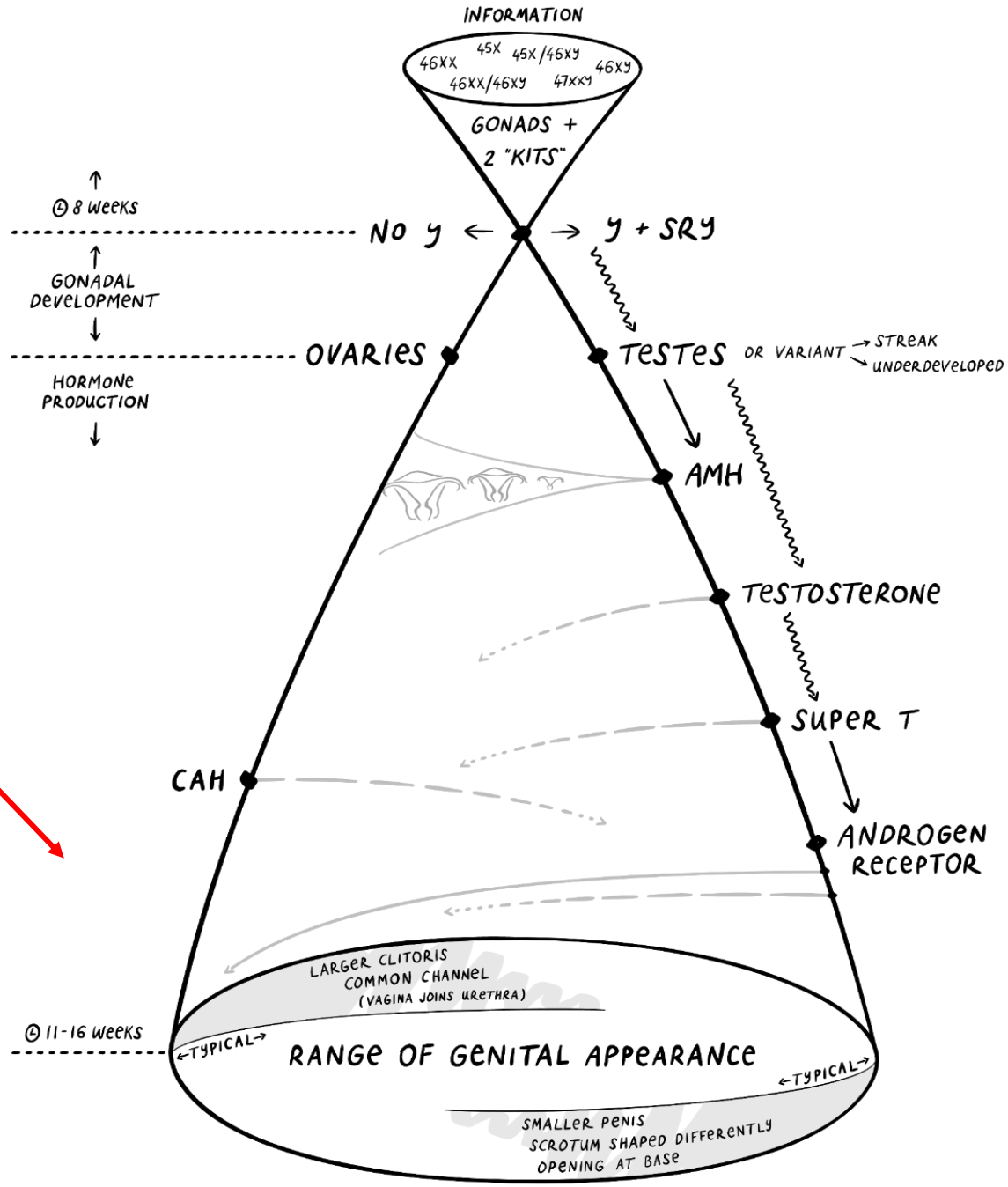
Before SuperT changes genital appearance, it needs to go through the 'Androgen Receptor Doors'.

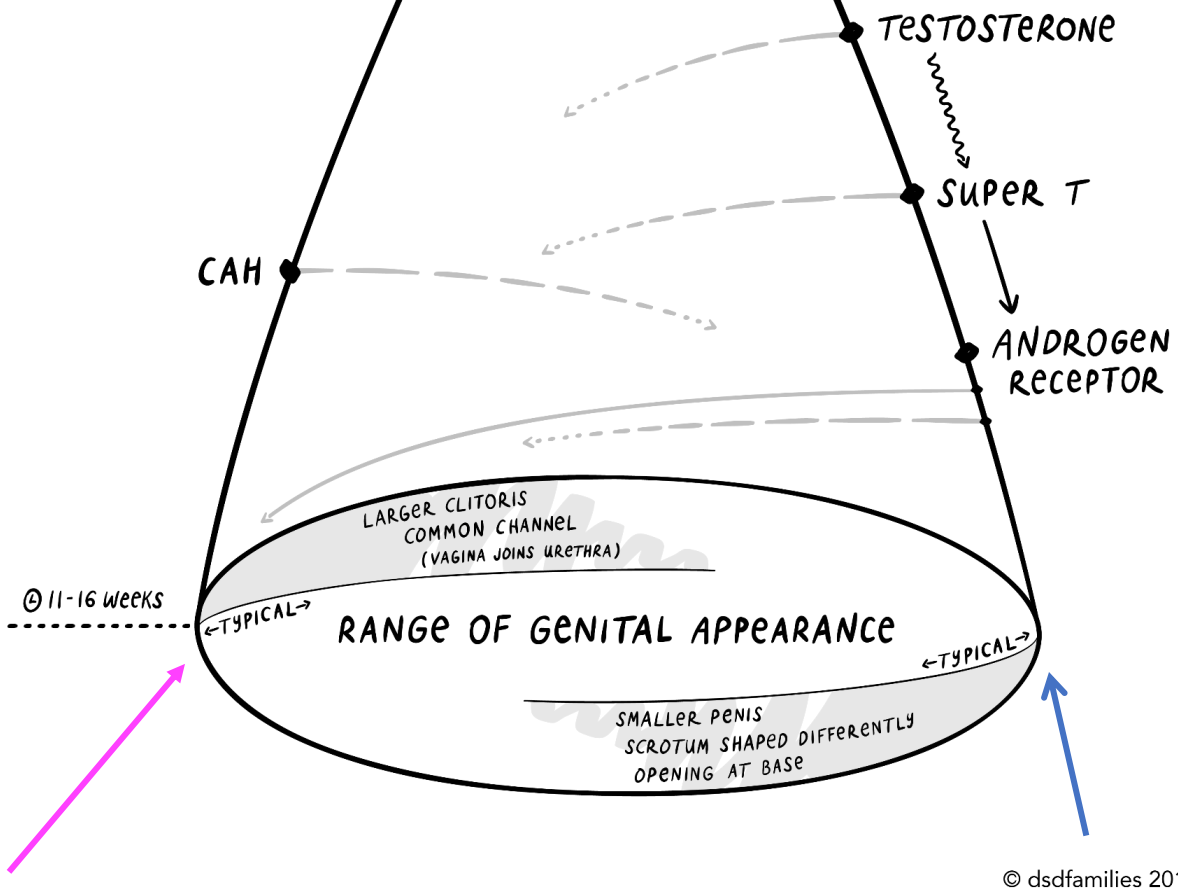
- Usually those doors are wide open and the SuperT rushes through.
- Sometimes the Androgen Receptor Doors are totally shut, and no SuperT gets through at all.
- And other times, the Androgen Receptor Doors are partially open; this can be anything from almost closed to quite open.

When gonads develop into ovaries, nothing much else happens.

The reproductive organs (womb, fallopian tubes and upper part of vagina) simply grow.

Sometimes, there can be a problem with the adrenal gland and this can lead to an overproduction of androgens (hormones like Testosterone) in girls with ovaries. This is a life-threatening medical condition called Congenital Adrenal Hyperplasia.

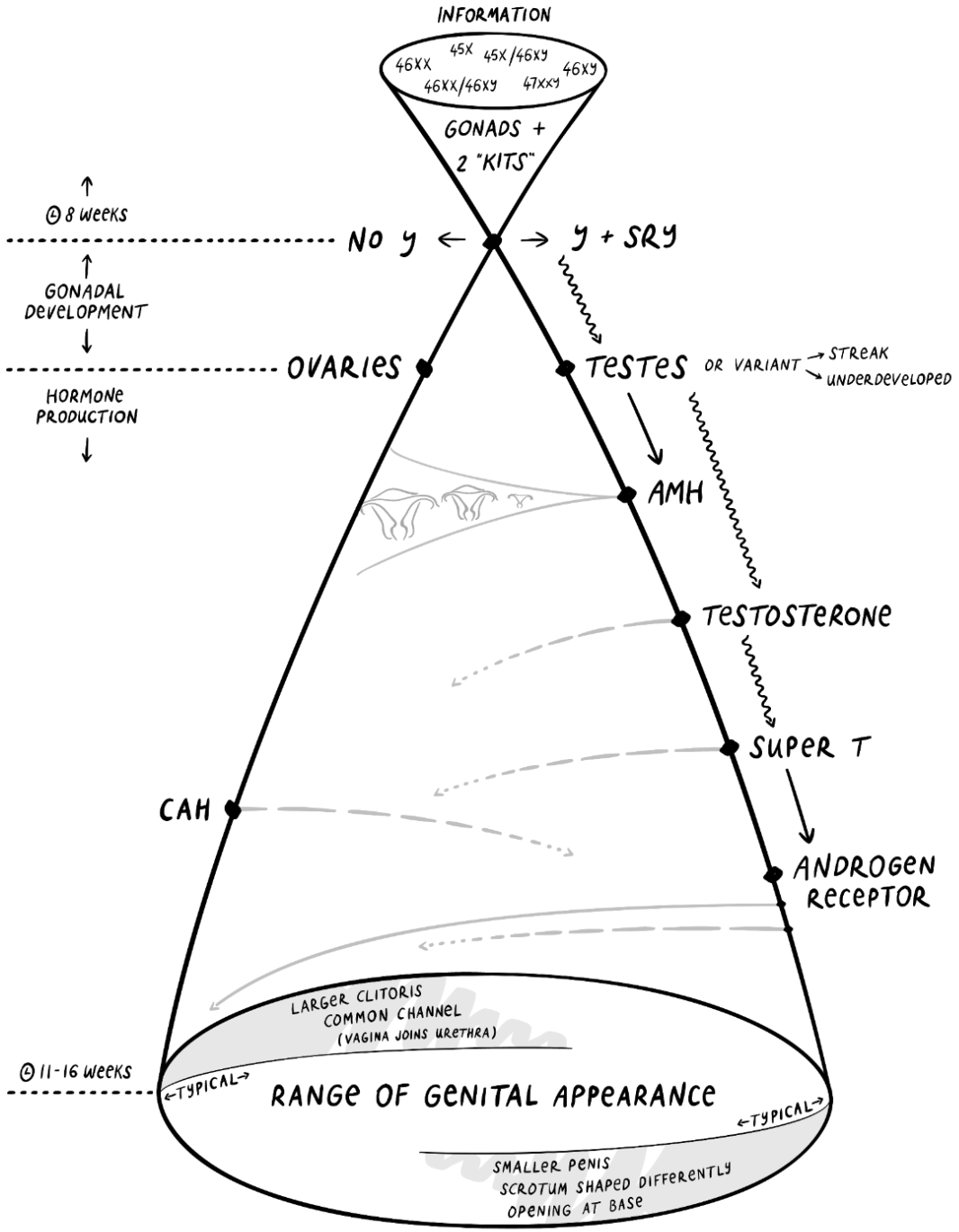




All vulvas look different and there is a huge range we can call ‘typical’.

The overproduction of T can make the clitoris grow larger than usual.
It can also affect the lower development of the vagina: the vagina can ‘join’ the urethra to form one ‘exit’ point.

All penises look different and there is a huge range we can call ‘typical’.
If less T has been produced (and if less SuperT has been produced, if androgen receptor doors were not fully open), the penis might look smaller than usual and sometimes the opening can be at the base of the penis, not at the tip.
Sometimes also the scrotum can look different.



Can you now draw and tell us YOUR Story of Sex Development?

Story of Sex Development

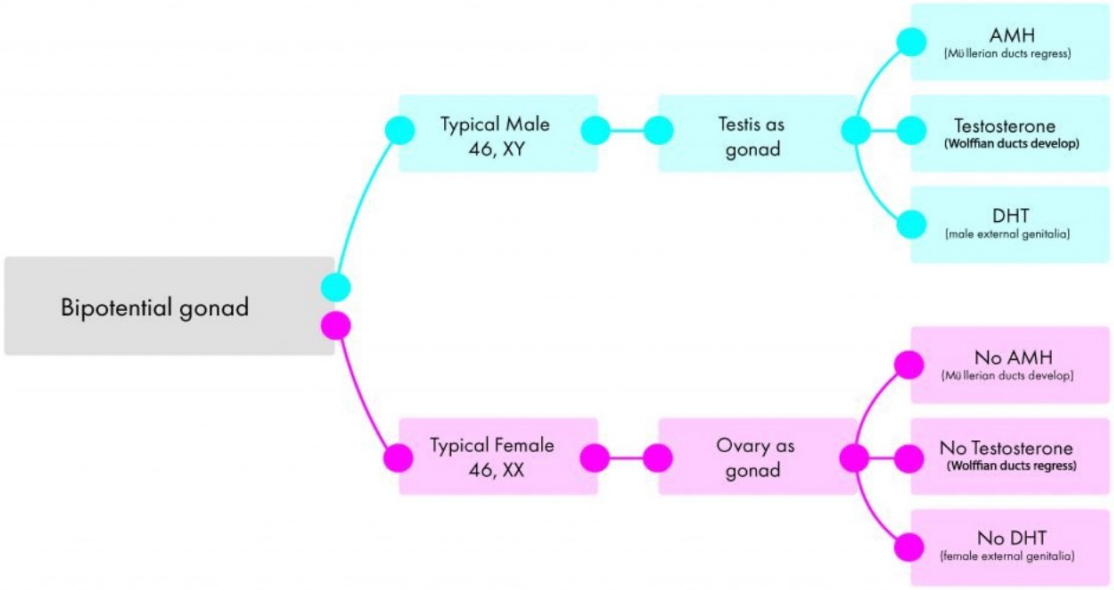
Davies, 2019

dsdfamilies

www.dsdfamilies.org

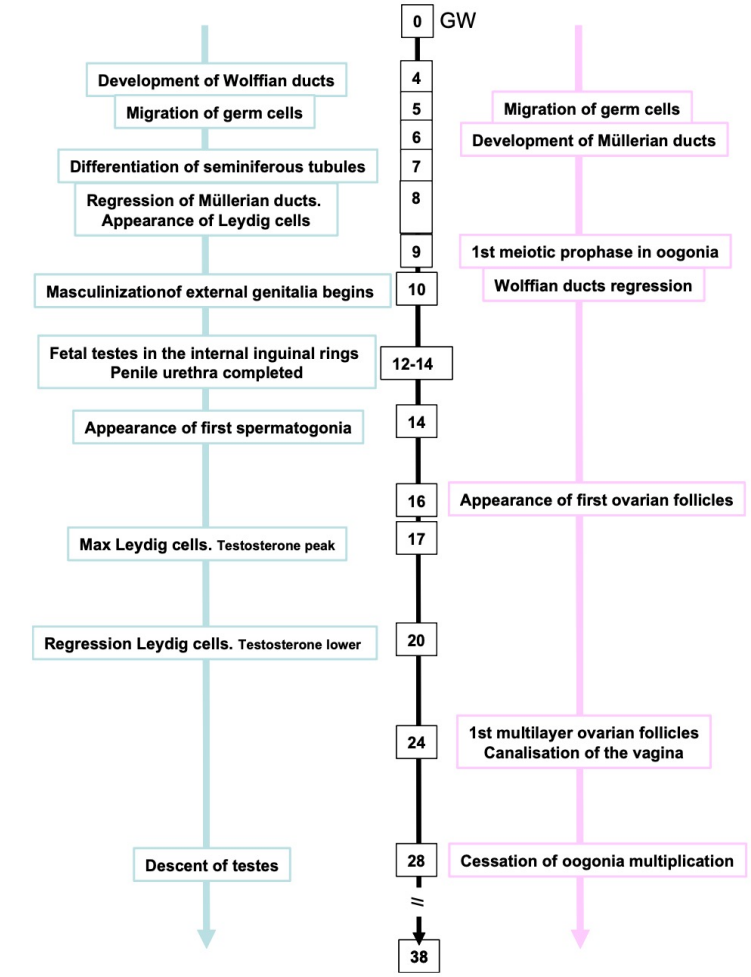
Concluding the story..

- Summary of embryological development



https://www.ogmagazine.org.au/20/4-20/intersex-variations-in-sex-characteristics/

- Illustration of sexual differentiation



Biason-Lauber, 2009

References

- Biason-Lauber, A. (2010). Control of sex development. *Best Pract Res Clin Endocrinol Metab, 24*(2), 163-186. doi:10.1016/j.beem.2009.12.002
- Bishop, R. (2010). Applications of fluorescence in situ hybridization (FISH) in detecting genetic aberrations of medical significance. *Bioscience Horizons, 3*(1), 85 - 95.
- Cool, J., & Capel, B. (2009). Mixed signals: development of the testis. *Semin Reprod Med, 27*(1), 5-13. doi:10.1055/s-0028-1108005
- Cunha, G. R., Robboy, S. J., Kurita, T., Isaacson, D., Shen, J., Cao, M., & Baskin, L. S. (2018). Development of the human female reproductive tract. *Differentiation, 103*, 46-65. doi:10.1016/j.diff.2018.09.001
- Davies, K. (2019). Disorders of Sex Development. In S. Llahana, C. Follin, C. Yedinak, A. Grossman, K. Davies, & M. F. Keil (Eds.), *Advanced Practice in Endocrinology Nursing* (Vol. 1, pp. 39 - 61). Switzerland: Springer.
- Grimaldi, C., & Raz, E. (2020). Germ cell migration-Evolutionary issues and current understanding. *Semin Cell Dev Biol, 100*, 152-159. doi:10.1016/j.semcdb.2019.11.015
- Hiort, O. (2013). The differential role of androgens in early human sex development. *BMC Medicine 11*(152), 1 - 7.
- Hiort, O. (2017). Normal and Variant Sex Development. In M. Legato (Ed.), *Principles of Gender Specific Medicine* (3rd ed., pp. 1 - 16): Elsevier.
- Hutson, J. M. (2012). Embryology of the human genital tract. In J. M. Hutson, G. L. Warne, & S. R. Grover (Eds.), *Disorders of Sex Development: An integrated approach to management* (1st ed.). Australia: Springer.

References

- Makela, J. A., Koskenniemi, J. J., Virtanen, H. E., & Toppari, J. (2019). Testis Development. *Endocr Rev, 40*(4), 857-905. doi:10.1210/er.2018-00140
- Sekido, R., & Lovell-Badge, R. (2009). Sex determination and SRY: down to a wink and a nudge? *Trends Genet, 25*(1), 19-29. doi:10.1016/j.tig.2008.10.008
- Turcu, A. F., & Auchus, R. J. (2015). Adrenal steroidogenesis and congenital adrenal hyperplasia. *Endocrinol Metab Clin North Am, 44*(2), 275-296. doi:10.1016/j.ecl.2015.02.002
- Telfer, E & Anderson, R (2019) The existence and potential of germline stem cells in the adult mammalian ovary Climacteric doi=10.1080/13697137.2018.1543264
- Vainio, S., Heikkila, M., Kispert, A., Chin, N., & McMahon, A. P. (1999). Female development in mammals is regulated by Wnt-4 signalling. *Nature, 397*, 405 - 409.
- Webster, S., & de Wreede, R. (2016). *Embryology at a glance* (2nd ed.). Oxford: Wiley Blackwell.
- Wisniewski, A. B., Chernausek, S. D., & Kropp, B. P. (2012). *Disorders of Sex Development: A guide for parents and physicians*. Maryland, USA: Johns Hopkins University Press.
- Yamada, G., Satoh, Y., Baskin, L. S., & Cunha, G. R. (2003). Cellular and molecular mechanisms of development of the external genitalia. *Differentiation, 71*(8), 445-460. doi:10.1046/j.1432-0436.2003.7108001.x
- Yeoh, P. (2019). Anatomy and Physiology of the Adrenal Gland. In S. Llahana, C. Follin, C. Yedinak, A. Grossman, K. Davies, & M. Keil (Eds.), *Advanced Practice in Endocrinology Nursing* (1st ed., Vol. 1, pp. 645 - 655). Cham: Springer.
- Zhu, YS & McGinley, J (2009) Disorders in male sexual differentiation: Molecular genetics, gender identity and cognition. In Rubin, RT & Pfaff, DW (Eds) Hormone / Behavior Relations of Clinical Importance. Academic Press.

Thank you

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