Estrogens from the fetus to the adult male

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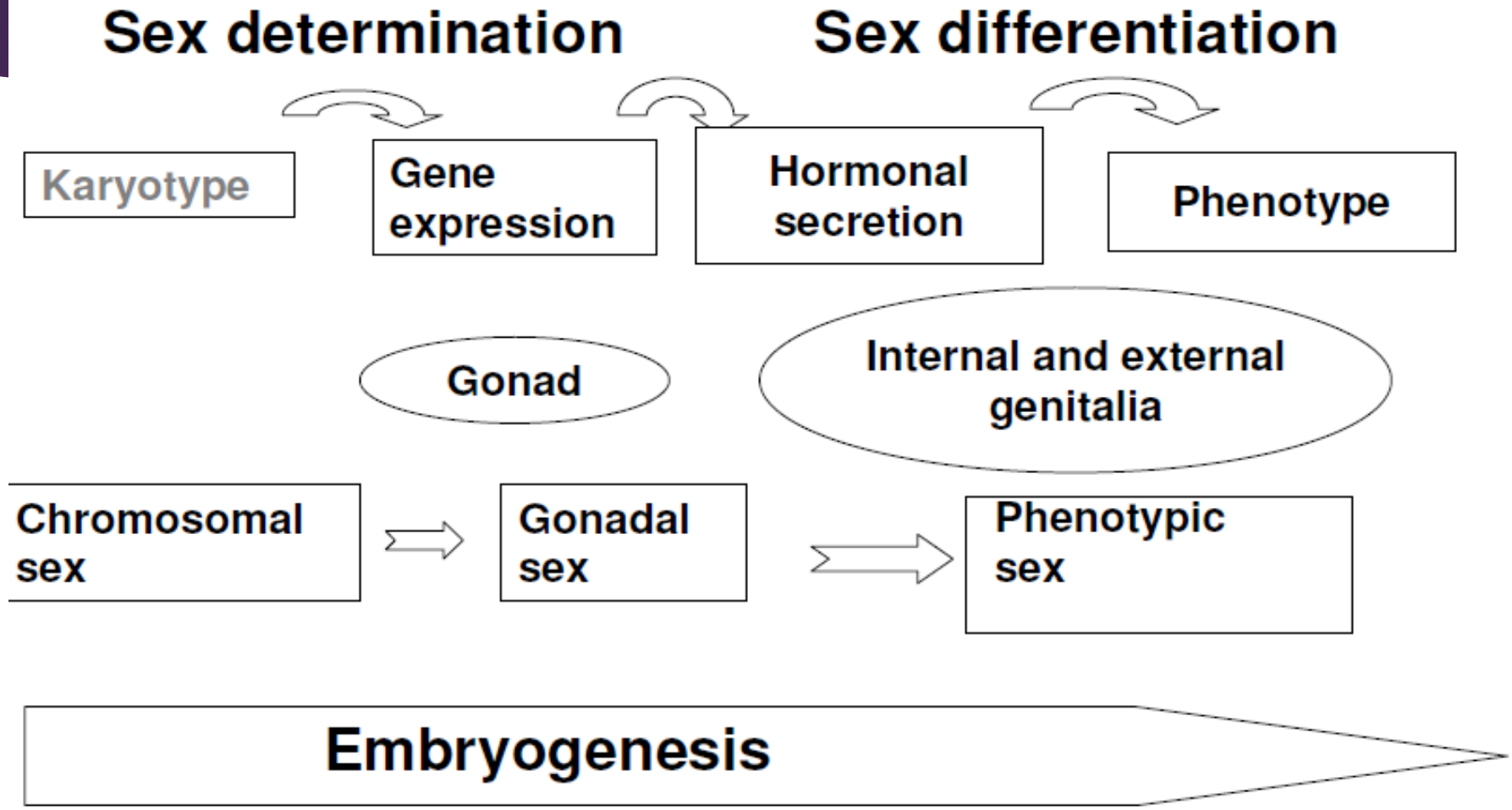
There is no conflict
of interest to disclose

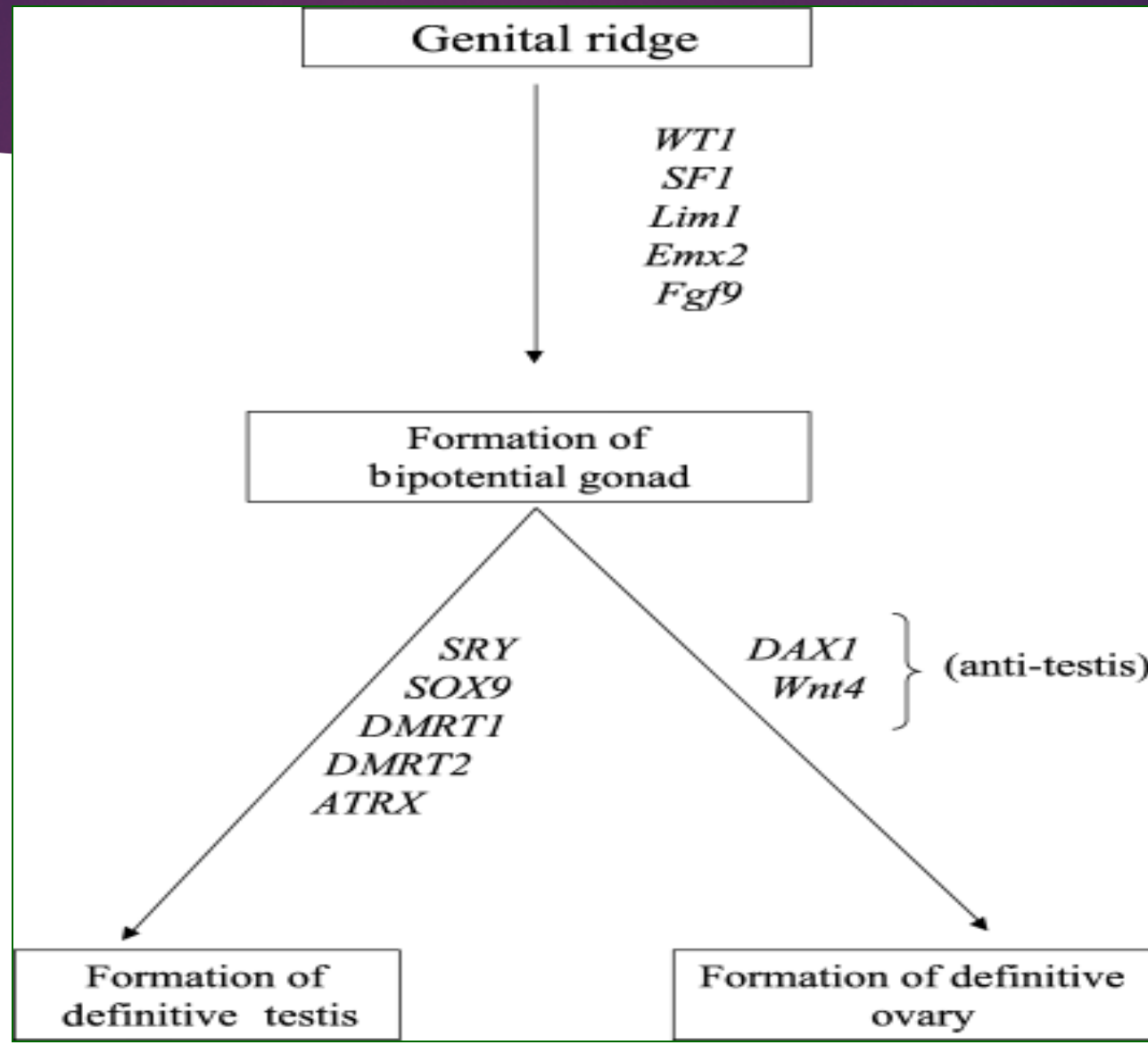
The role of androgens in the male

- The role of androgens in the male, in
  - Sexual differentiation
    - Testicular descent
      - Future fertility
    - Is undisputable.
- The role of estrogens has only come to light during recent years, mainly due to the estrogenic effect of the Endocrine diruptors

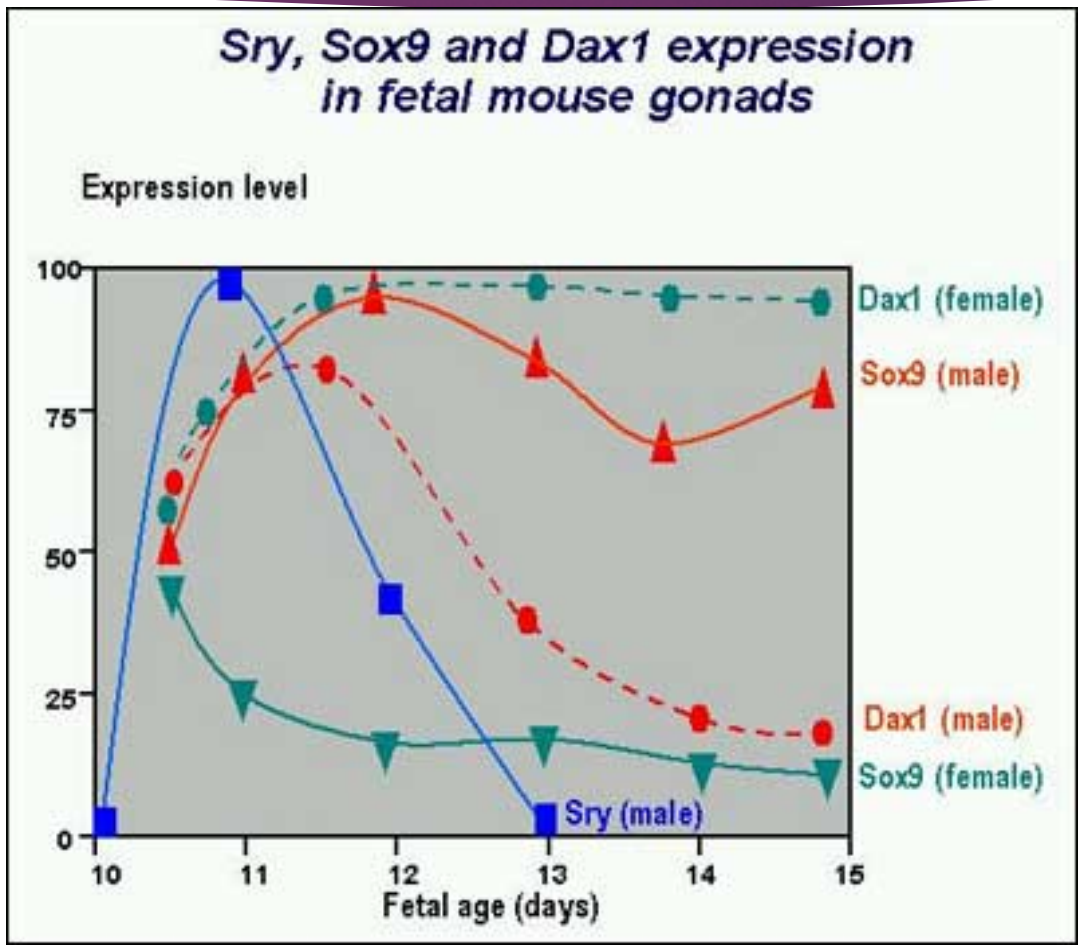
Sex determination and sex differentiation



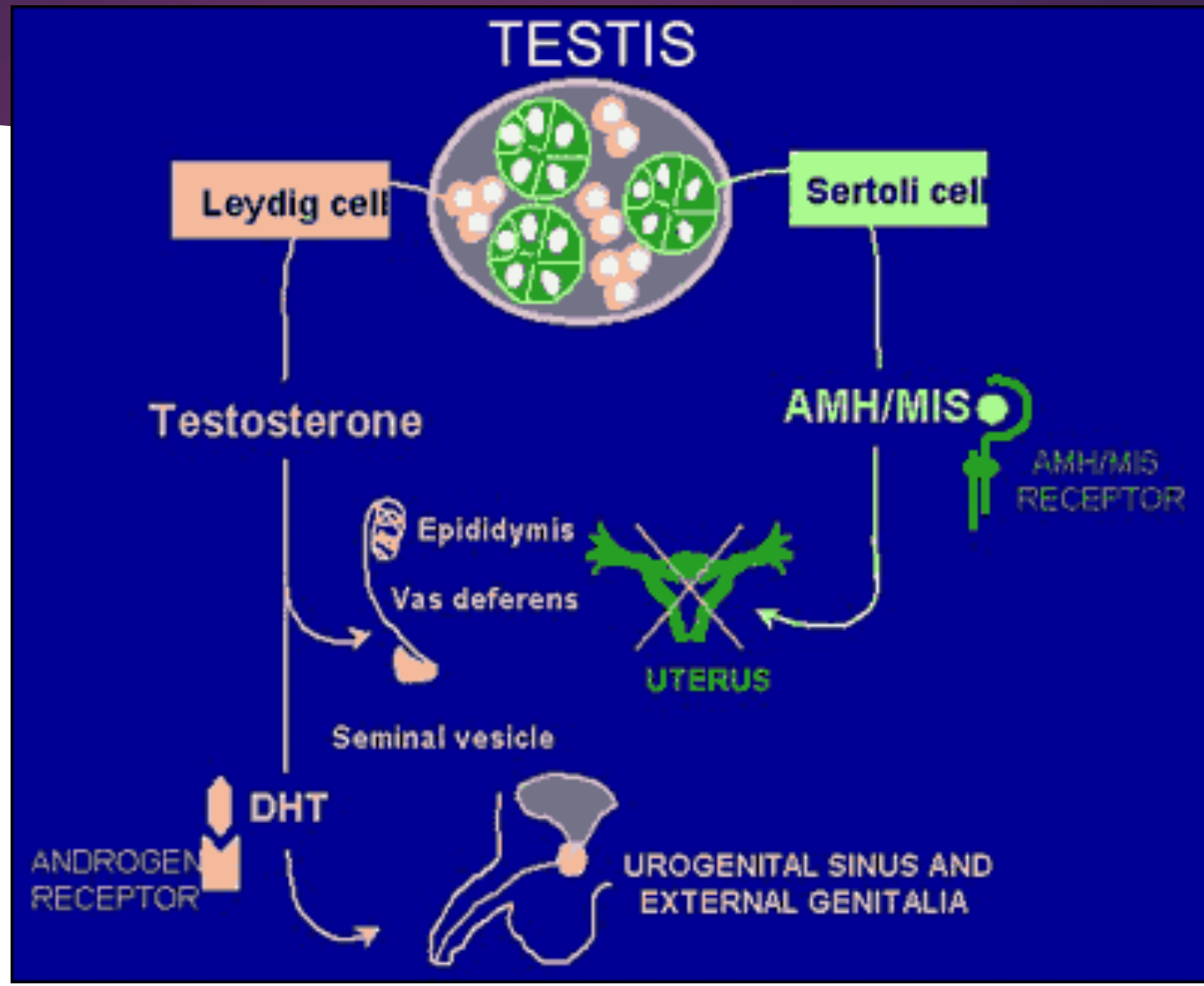
Sex Determination



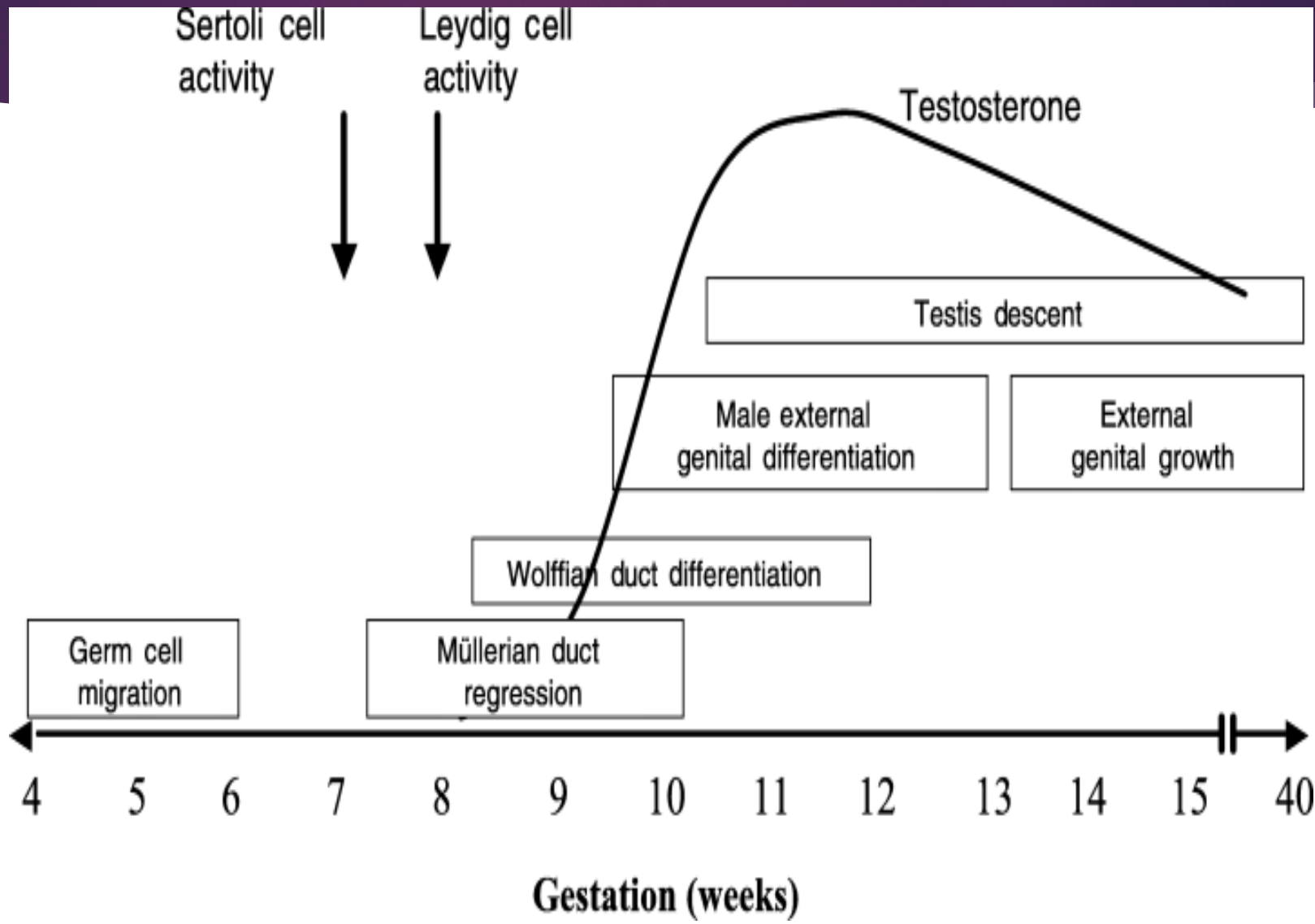
Temporal expression of specific transcription factors during sexual differentiation

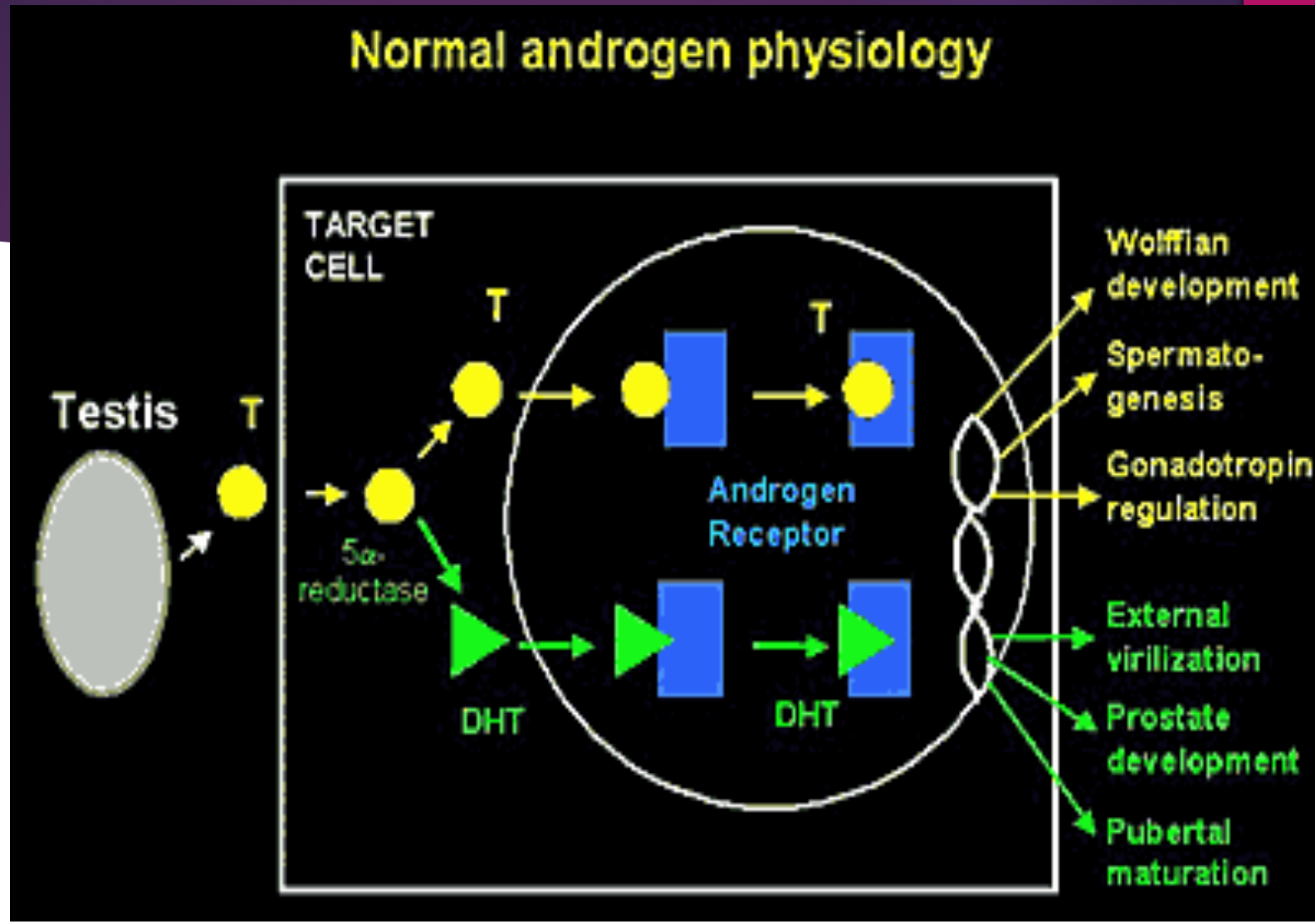


Sex differentiation

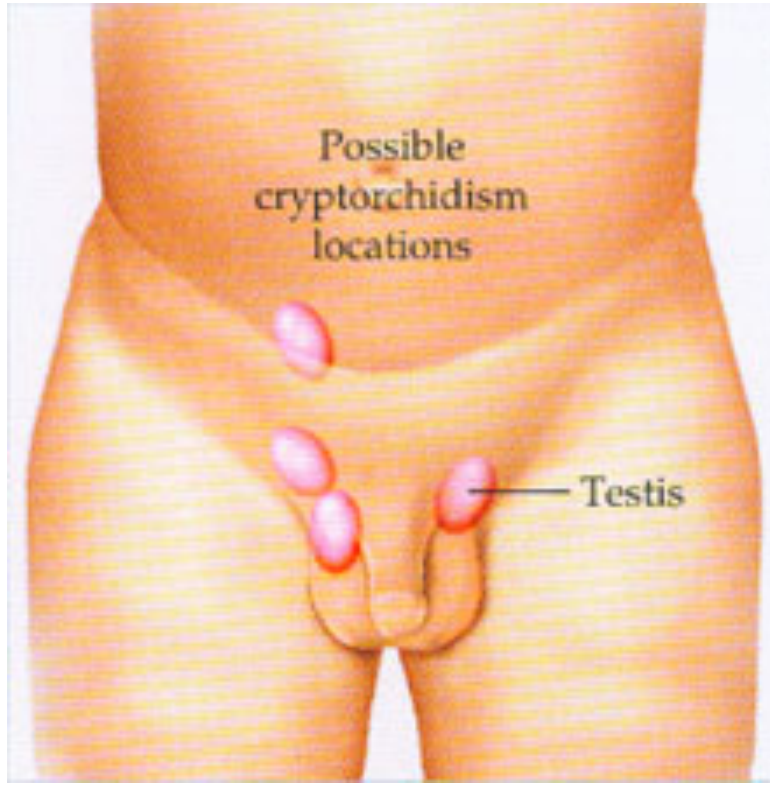


The role of testosterone in the male




Normal androgen physiology
TARGET CELL
Testis
T
T
T
5α-reductase
Androgen Receptor
DHT
DHT
Wolffian development
Spermato-genesis
Gonadotropin regulation
External virilization
Prostate development
Pubertal maturation

The role of testosterone in testicular descent



Normal sequence of events

- **At birth, gonadotropins, testosterone and AMH levels are transiently low and subsequently increase.**
- **FSH stimulates Sertoli cell proliferation and AMH production.**
- **The onset of AMH secretion during fetal life and the maintenance of its basal levels are gonadotropin-independent. However, serum AMH is low in patients with congenital hypogonadotropic hypogonadism and increases in response to exogenous FSH administration, indicating that AMH is a useful marker of FSH action in the prepubertal testis.**

Background information

- ***The neonatal-mid-infancy surge in pulsatile GnRH secretion***
  - is attributable to an increase in GnRH pulse amplitude
  - Is associated with a rapid expansion of Leydig and Sertoli cell populations
  - Leading to concomitant surge in Testosterone, Inhibin B and AMH production
  - And increase in testicular volume
- **Boys with congenital hypogonadotropic hypogonadism do not activate this process.**
- **Potential cause of azoospermia and infertility in adult life is deficient proliferation of immature Sertoli cells before and during puberty due to FSH absence.**

Evolution of the testicular volume

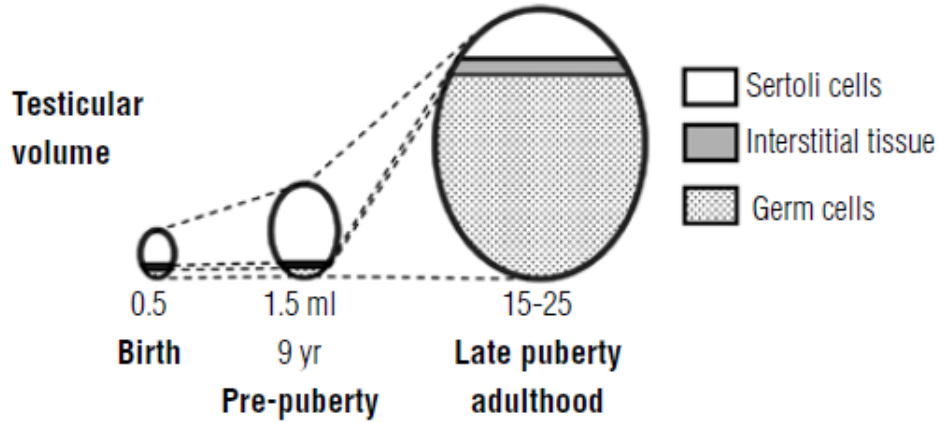


Figure 2. Schematic ontogeny of the evolution of testicular volume from birth to adulthood. Seminiferous tubules (Sertoli + germ cells) are always the major component of the testis. From birth and during the whole prepubertal period (i.e. until ages 9-14 yr, Tanner stage 1), seminiferous tubule volume depends mainly on Sertoli cells, whereas the significant increase in testicular volume during pubertal development (i.e. between Tanner stages 1 and 5) is mainly due to germ cell proliferation. Reprinted with permission from: Rey R. Regulation of spermatogenesis. Endocrine Development. 2003;5:38-55. Söder O (ed.): The Developing Testis. Physiology and Pathophysiology. Copyright S. Karger A. G., Basel, 2003.

Seminiferous tubules (Sertoli + germ cells) are the major component of the testis

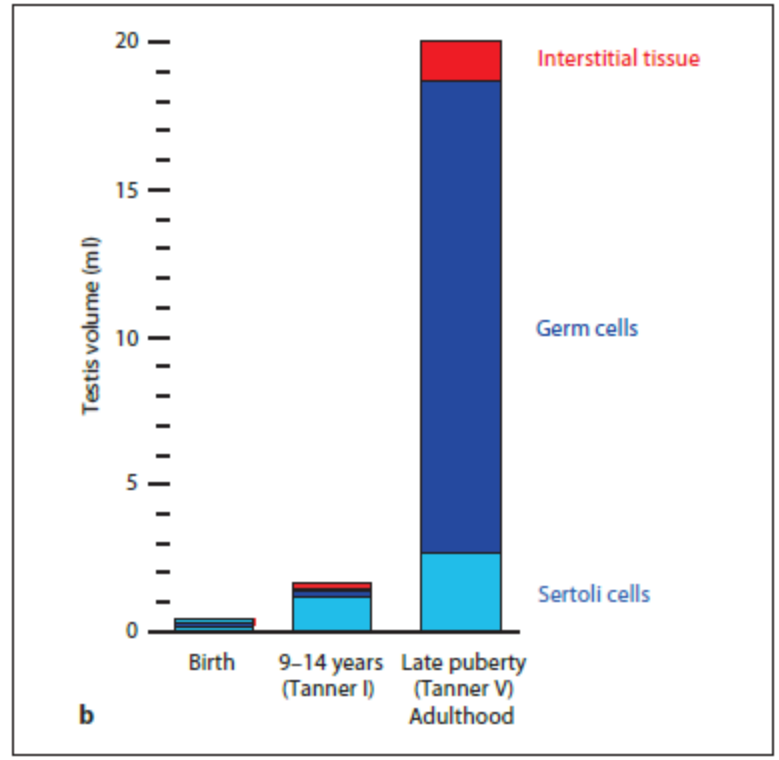
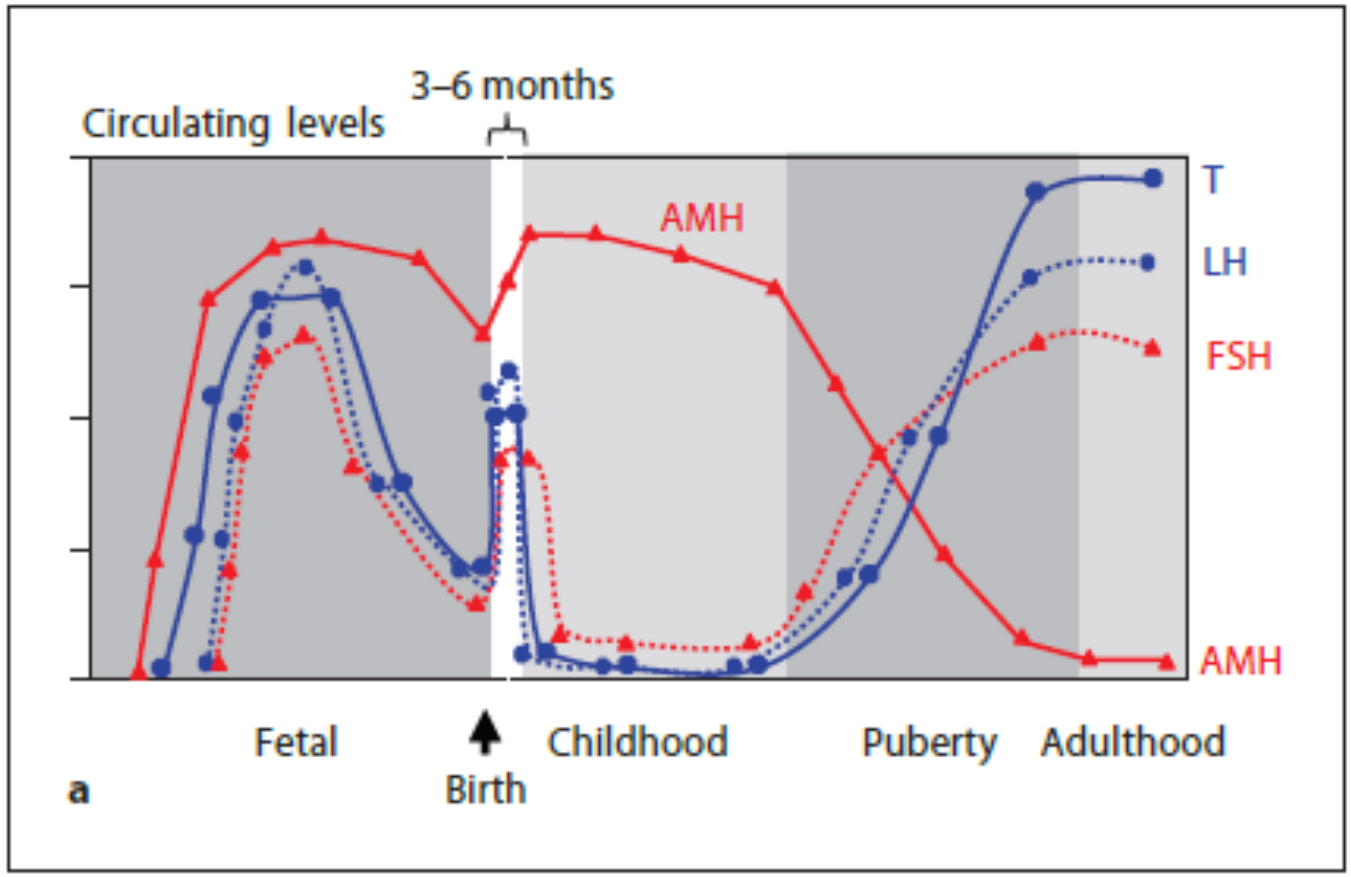


Fig. 1. a Schematic ontogeny of circulating levels of gonadotrophins, testosterone (T) and AMH in the male. **b** Schematic ontogeny of the evolution of testicular volume from birth to adulthood. Seminiferous tubules (Sertoli + germ cells) are always the major component of the testis. From birth and during the whole prepubertal period (i.e., until ages 9–14 years, Tanner stage I), seminiferous tubule volume depends mainly on Sertoli cells, whereas the significant increase in testicular volume during pubertal development (i.e., between Tanner stages I and V) is mainly due to germ cell proliferation.

Normal circulating levels of LH, FSH, Testo and AMH from fetal life to adulthood



The inverse relationship between Testosterone and AMH

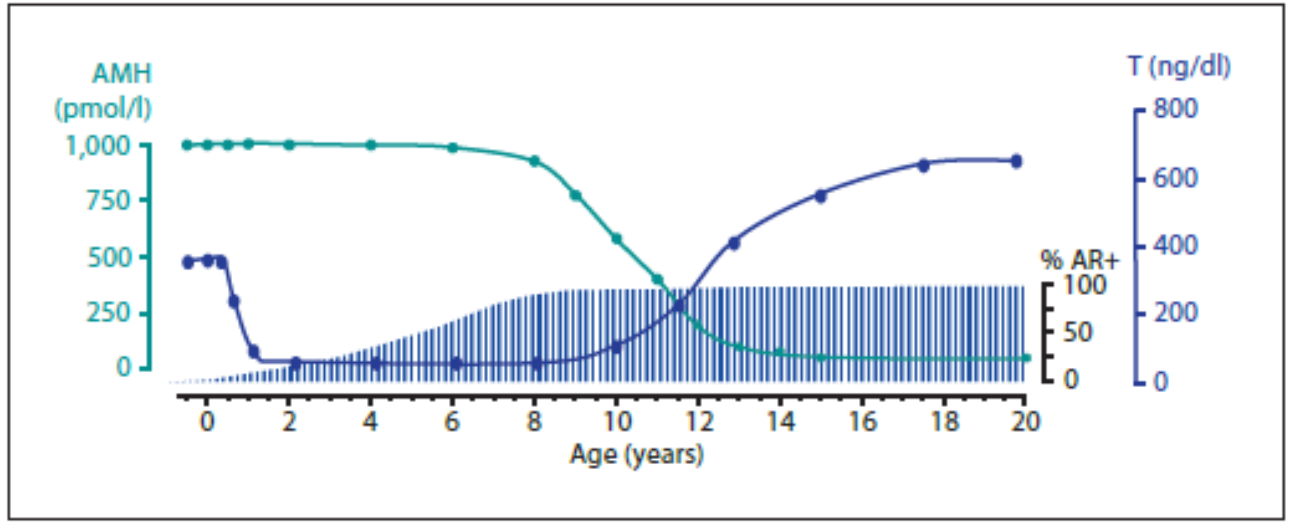


Fig. 2. Relationship between serum testosterone, androgen receptor (AR) expression in Sertoli cells and serum AMH from birth to puberty. AR expression in Sertoli cells is represented as the percentage of Sertoli cells with AR immunolabelling [data from 28, 45].

Normal male fertility

- It is well established that normal male fertility depends on spermatogenesis, the process of proliferation and differentiation of germ cells into mature spermatids and is under hormonal control.
- Testosterone and FSH and LH are key players in spermatogenesis, estradiol is now recognized to play an important role in testicular physiology and spermatogenesis too.

Background Information

- **During the last decades it has been increasingly evident that exposure to environmental agents with estrogenic activity both during intrauterine life and later on may have adverse effects on human reproductive health.**
- Both hypospadias and cryptorchidism but also testicular cancer are increasing in recent years.
- **On the other hand we face a decline of human fertility and an increased number of disorders of the genitourinary tract in males especially in industrialised areas.**

The role of Estrogens in the male

- Estrogens role during fetal life
- Endogenous production of estrogens
- The role of Exogenous estrogens/xenoestrogens
- Actions of estrogens on the testis
- Estrogens role in adult life
- Estrogens and future fertility
- Estrogens and cancer risk

Estrogens and reproductive health

Estrogens in male germ cells

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Spermatogenesis 1:2, 90-94; April/May/June 2011; © 2011 Landes Bioscience

Estrogens in the male

- Estrogens (oestrone and estradiol) are synthetized in the gonads from Androstendione or testosterone by the Aromatase P450 enzyme.
- Aromatase deficiency in a 46,XY newborn has been described to cause hypospadias and cryptorchidism.
- Elevated estrogen levels may also be a cause of hypospadias.

Estrogens in the male

- Estrogens locally produced within the seminiferous epithelium through the irreversible transformation of androgens (C18) into estrogens (C18) by the aromatase are implicated in germ cell development and spermiogenesis.

Background information

- The importance of estrogens in spermatogenesis is **highlighted by the fact that E2 is produced locally in the adult testis by**
- **Most of the germ cells**
- **The Sertoli cells**
- **The Leydig cells**
- **Through the conversion of testosterone to E2 by the aromatase cytochrome P450.**

Estrogens in the different testicular cell populations

- **In fetal and immature animals, Sertoli cells are the main source of estrogens, and the expression of aromatase in Leydig cells is very low.**
- **Through development, the cellular sites of aromatization change and aromatase is mostly localized in Leydig cells, while in the adult rat aromatase expression is low in Sertoli cells.**

Estrogens in germ cells

- Adult mouse germ cells express a functional aromatase, and estradiol output is equivalent to that of Leydig cells, representing 60% of that contributed by the whole testis.
- Aromatase activity is much higher in late haploid germ cells than in less differentiated germ cells, illustrating that quiescent cells can regulate their fate during development and spermatogenesis.

Germ cell-derived estrogens in reproduction

- The importance of germ-cell derived estrogens on male reproductive function has been demonstrated by aromatase knockout models (ArKO).
- Male ArKO develop normally and are able to breed and to produce litters. However, after the age of 5 months they present with failure of spermatogenesis and by one year they are infertile.
- There is a blockage of germ cell maturation at the spermatid stage.

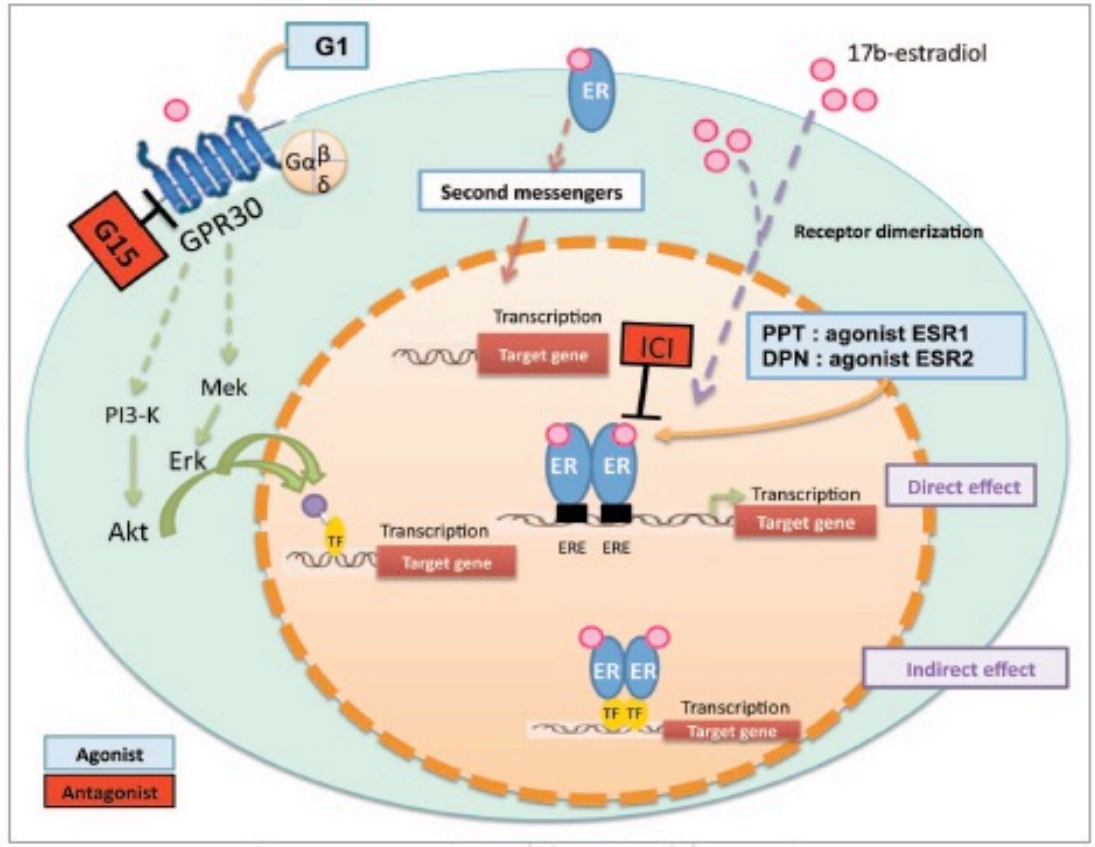
Human and animal data

- In patients with aromatase deficiency, impaired sperm motility and germ cells arrest (at the spermatid stage) was observed, demonstrating a putative link between the lack of estrogen activity and infertility in men.
- Exposure of adult male rats to a high phytoestrogen diet disrupts spermatogenesis via an increase in germ cell apoptosis.
- Overexpression of aromatase taking place either during fetal life or puberty leads to male infertility to 50-100% of cases.

Cellular localization

- A high level of aromatase is detected in the Golgi complex of the developing spermatid.
- The acrosome biogenesis is an estrogen-dependent process.
- A transmembrane receptor GPR30 is present in human and rodent testicular cells and is involved in the proliferation inducing effects of estrogens.
- Spermatogenesis is under the control of estrogens at various levels

Estrogens in the testis



igure 1. A schematic illustrating estrogen targeting in a testicular cell via genomic and non-genomic pathways involving estrogen receptors (ERs) nd GRP30, respectively. G_s, agonist of GPR30; G15, antagonist of GPR30; PPT, agonist of ESR1; DPN, antagonist of ESR2; TF, transcription factors; ER, strogen receptors; ICI, selective estrogen inhibitor (ICI 182780).

Role of estrogens in **Spermatogenesis**

- In human seminiferous tubules cultures a direct involvement of estrogens in preventing germ cell apoptosis has been demonstrated.
- Exposure of adult male rats to high phytoestrogen diet disrupts spermatogenesis by increasing germ cell apoptosis

  - Pentikainen V,… Dunkel L. JCEM, 2000;85:2057
    - Assinder et al, Reproduction, 2007;144:11
      - Robertsonn Km,PNAS, 1999;96:7986

Effect of estrogen receptor-subtype-specific ligands on fertility in adult male rats

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Cellular effects of estrogens

- The cellular effects of estrogens are mediated through the respective receptors, ERa and ERβ.
- Complete ERs knockout mice are infertile
- It seems that estrogens in adult life may have a role in maintaining male fertility in adulthood
- Although normal estrogen signaling through its receptor is important in maintaining spermatogenesis and male fertility, overactivation, as in the case of agonist treatment may be detrimental

Estrogen receptors localization

- Androgen receptors are mostly localized in somatic cells, while estrogen receptors are found in most testicular cells, including germ cells.
- Ers are found throughout the spermatozoon and intensively localized within the mitochondria.
- In humans, estrogens have been found in ejaculated spermatozoa and estrogens seem to be related to the quality (such as motility) of sperm cells.

Conclusion

There is a delicate balance between estrogens and androgens to maintain normal testicular physiology and reproductive function with aromatase playing a crucial role in these cellular events

Estrogens and hypospadias

- **From animal studies, it has been demonstrated that estrogens play a crucial role in:**
- **the positioning of the urethral orifice**
- **Determining elasticity of the urethral meatus**
- **Facilitating epithelial-epithelial fusion events during distal urethra/urogenital sinus and prepuce formation**
  - Cuhna et al, Nat Rev Urol, 2015

Estrogen receptors in Hypospadias

- ERa and ERβ are expressed in most cells of the male urethra.
- Various polymorphisms of ERs have been reported in hypospadias
- Factors that affect the level of activity of ERs may also play a role
- Certain environmental exposures may create epigenetic changes increasing the hypospadias risk for generations to come.

Developmental origin of prostate cancer risk

RESEARCH ARTICLE

Developmental Exposure to Estrogen Alters Differentiation and Epigenetic Programming in a Human Fetal Prostate Xenograft Model

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Estrogens and cancer risk

Testosterone plays an important role in sex differentiation and normal development of the fetus and newborn.

In the male, the balance between testosterone and estradiol is thought to be an important mediator of prostate disease.

From animal studies it has been shown that neonatal estrogen exposure plays a role in prostate cancer.

Prostate cancer is the most common non-cutaneous cancer in the male

Estrogens and prostate risk

- By using human fetal prostate tissue it has been demonstrated that early life estrogen exposure may lead to gene expression and epigenetic modifications related to prostate carcinogenesis.
- From animal studies it has been demonstrated that fetal and perinatal periods are highly susceptible to endocrine disruption.
- **"Hormonal imprinting hypothesis"**, highlighting the priming effects of early life exposure to estrogenic compounds on prostate tissue.

Estrogens and prostate risk

- By using human fetal prostate tissue it has been demonstrated that the human fetal prostate is more resistant to estrogenic exposures compared to previous studies performed in rats, highlighting the difficulty of extrapolating animal data to human carcinogenesis.
- Estrogen exposure-related alterations in DNA methylation primarily occurred in the stroma, emphasizing the role of this compartment in carcinogenesis.

Estrogen effects on male reproductive health

REPRODUCTION

REVIEW

Estrogen effects on fetal and neonatal testicular development

Géraldine Delbès[1,2,3], Christine Levacher[1,2,3] and René Habert[1,2,3]

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Correspondence should be addressed to R Habert who is now at Unitè Gamètogenèse et Gènotoxicitè, Univ Paris 7, Denis Diderot, CEA, INSERM U566, CEA/DSV/DRR/SEGG/LDRG, Bat. 5A, RDC, Route du Panorama, 92265 Fontenay-aux-Roses, France; Email: rene.habert@cea.fr

Maternal Pregnancy Levels of Polychlorinated Biphenyls and Risk of Hypospadias and Cryptorchidism in Male Offspring

Katherine A. McGlynn,[1] Xuguang Guo,[2] Barry I. Graubard,[1] John W. Brock,[3] Mark A. Klebanoff,[4] and Matthew P. Longnecker[5]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA; [2]Westat, Inc., Durham, North Carolina, USA; [3]National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [4]Division of Epidemiology, Statistics, and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, Rockville, Maryland, USA; [5]Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA

Environmental Health

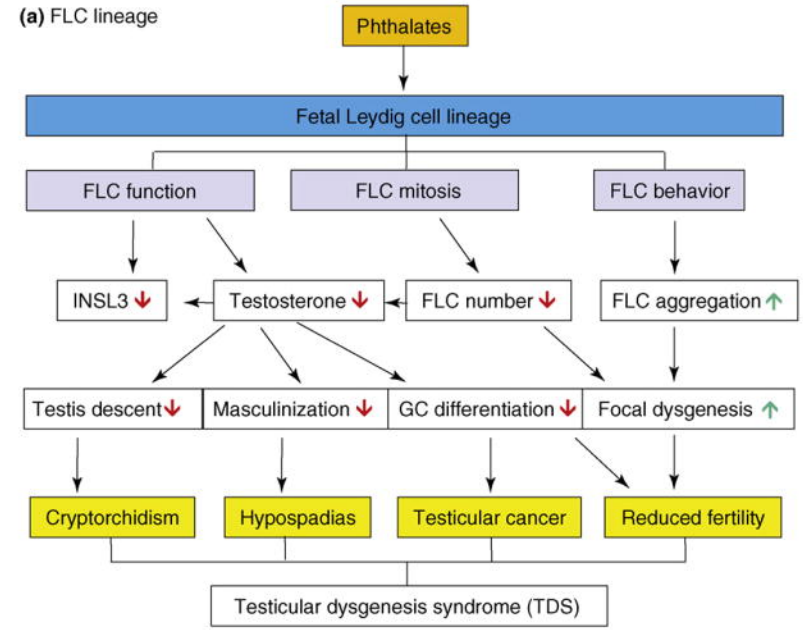
BioMed Central

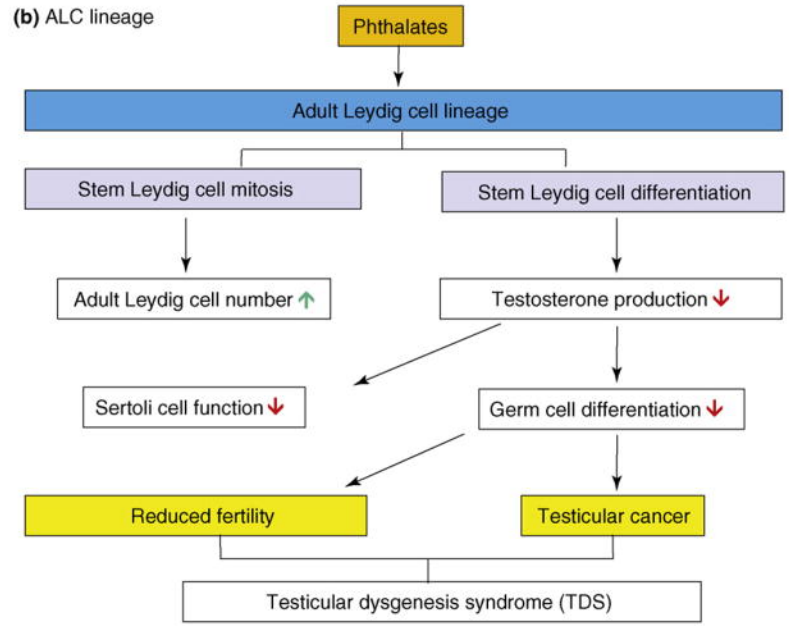
Research

Open Access

Urogenital abnormalities in men exposed to diethylstilbestrol *in utero*: a cohort study

Julie R Palmer*[1], Arthur L Herbst[2], Kenneth L Noller[3], Deborah A Boggs[1], Rebecca Troisi[4,5], Linda Titus-Ernstoff[5], Elizabeth E Hatch[6], Lauren A Wise[1], William C Strohsnitter[3] and Robert N Hoover[4]





TRENDS in Endocrinology & Metabolism

Clinical Endocrinology (2009) **71**, 459–465 doi: 10.1111/j.1365-2

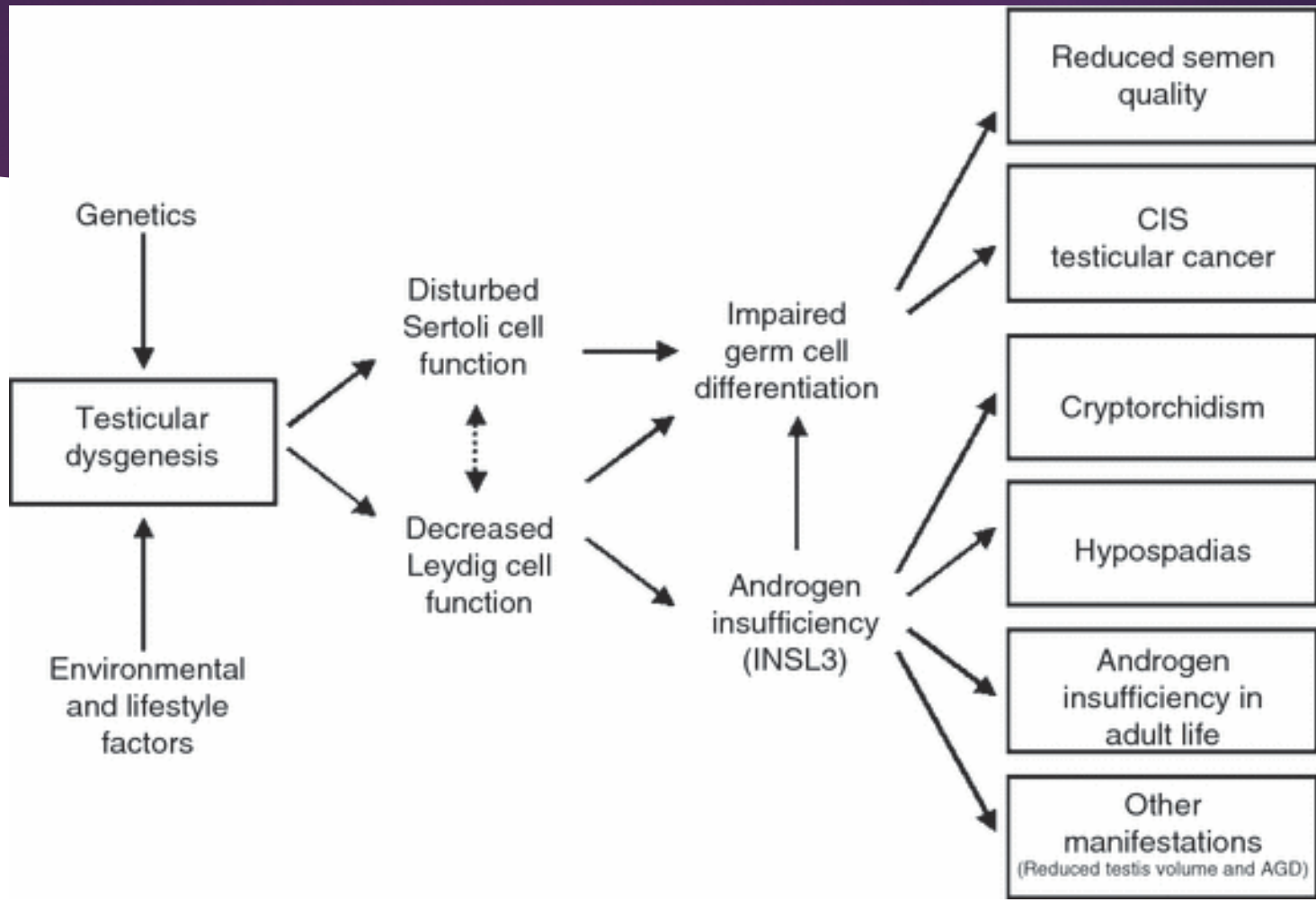
REVIEW ARTICLE

Testicular dysgenesis syndrome: foetal origin of adult reproductive problems

Christine Wohlfahrt-Veje, Katharina M. Main and Niels Erik Skakkebæk

University Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark

The testicular dysgenesis syndrome



Clin Endocrinol, Oct 2009

Conclusions

- **Estrogens in the male have major roles** in:
- Germ cell development and future fertility
- Testicular development leading to the testicular dysgenesis syndrome
- Development of the urethral plate and risk of hypospadias
- Prostate cancer risk

The role of estrogens in the male is crucial!

I thank you for your attention!