

# **BIOSYNTHESIS OF STEROID HORMONES**

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# STEROID HORMONES

- Progestins (21 C)
- Glucocorticoids (21 C)
- Mineralocorticoids (21 C)
- Androgens ( 19 C)
- Estrogens (18 C)

<b>Steroid class</b>	<b>Source</b>	<b>Stimulated by</b>	<b>Example</b>
Progestins	Corpus luteum, placenta	LH	Progesterone
Glucocorticoids	Adrenal cortex	ACTH	Cortisol
Mineralocorticoids	Adrenalcortex (zona glomerulosa)	Angiotensin II, ACTH	Aldosterone
Androgens	Leydig cells (major) Adrenal cortex (minor)	LH, ACTH	Testosterone
Estrogens	Ovarian follicle	FSH	Estradiol

Synthesized from its precursor – **cholesterol**, in

- adrenal cortex (mineralocorticoids, glucocorticoids, androgens)
- testes, ovaries ( sex hormones)
- skin, liver, kidney (calcitriol / vit D3)

Secreted from sites of synthesis – transported to the target organ – cross the cell membrane of target organ – bind to specific receptors in cytoplasm or nucleus

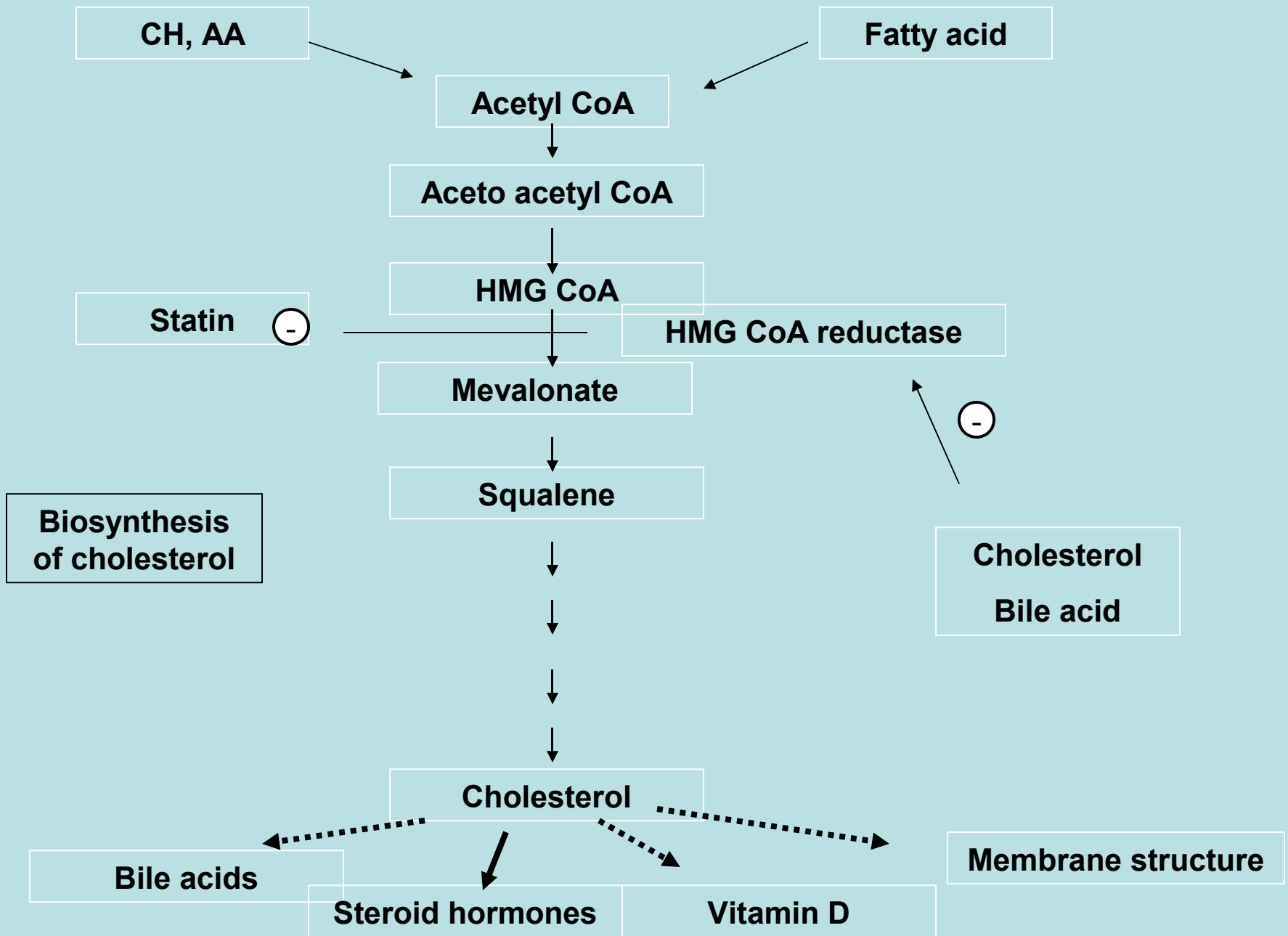
Transported in blood – bound to **globulin** – ***corticosteroid-binding globulin (CBG), sex hormone-binding globulin (SHBG)***

## Cholesterol for synthesis of steroid hormones

- Plasma cholesterol
- Synthesis in situ from acetyl CoA via mevalonate and squalene

Cholesterol in adrenal is esterified and stored in cytoplasmic droplets

Stimulation of adrenal by ACTH – activated esterase – free cholesterol is transported into mitochondria – mitochondrial cytochrome P450 cleave the cholesterol side chain – convert into pregnenolone



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**Fig 1. Biosynthesis of cholesterol**

- Cleavage of the side chain of cholesterol – involved sequential hydroxylation at C22 and C20 – then followed by side chain cleavage – give 21 C steroid
- All mammalian steroid hormones are formed from cholesterol via pregnenolone – through a series of reaction in mitochondria or endoplasmic reticulum adrenal cells

# ADRENAL STEROID HORMONES

- Mineralocorticoids
- Glucocorticoids
- **Androgens**



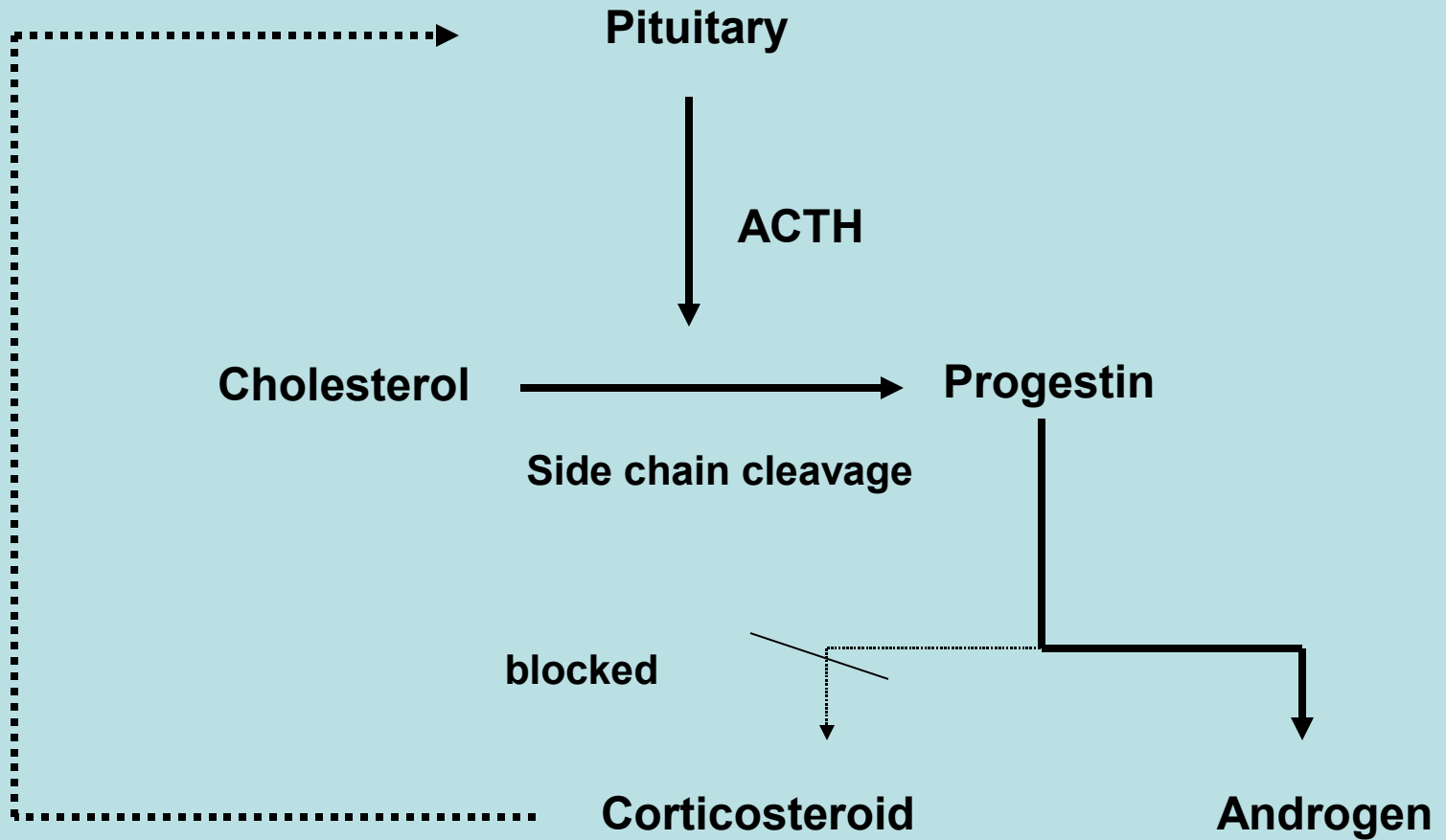


# ANDROGEN SYNTHESIS

- Major androgen in adrenal cortex is DHEA
- Most of 17OH-pregnenolone followed the glucocorticoid pathway
- Adrenal androgen production increased markedly if glucocorticoid synthesis is impaired – in adrenogenital syndrome (congenital adrenal hyperplasia)

## Congenital adrenal hyperplasia

- Incidence 1/10.000
- Caused by deficiency of hydroxylases required for synthesis of glucocorticoid
- Glucocorticoid level are deficient – ACTH release disinhibited – causes adrenal hyperplasia and stimulation of desmolase – overproduce of progesterin - diverted into androgen synthesis
- The disorder produces ambiguous external genitalia in girls or pubertal precoc in boys



**Fig 3. Overproduce androgen in congenital adrenal hyperplasia**

# Progestin

- Synthesis is initiated by side chain cleavage of cholesterol by mitochondrial desmolase – produced pregnenolone – converted to progesterone by microsomal and cytoplasmic enzyme
- Progesterone – the major end product in corpus luteum & placenta
- Other endocrine gland – convert pregnenolone & progesterone to other steroid hormones

# Corticosteroids

- Distinguished from progestins by the presence of additional OH groups
- The OH groups are introduced by monooxygenase reaction
- The reaction require cytochrome P450

# ADRENAL ANDROGEN

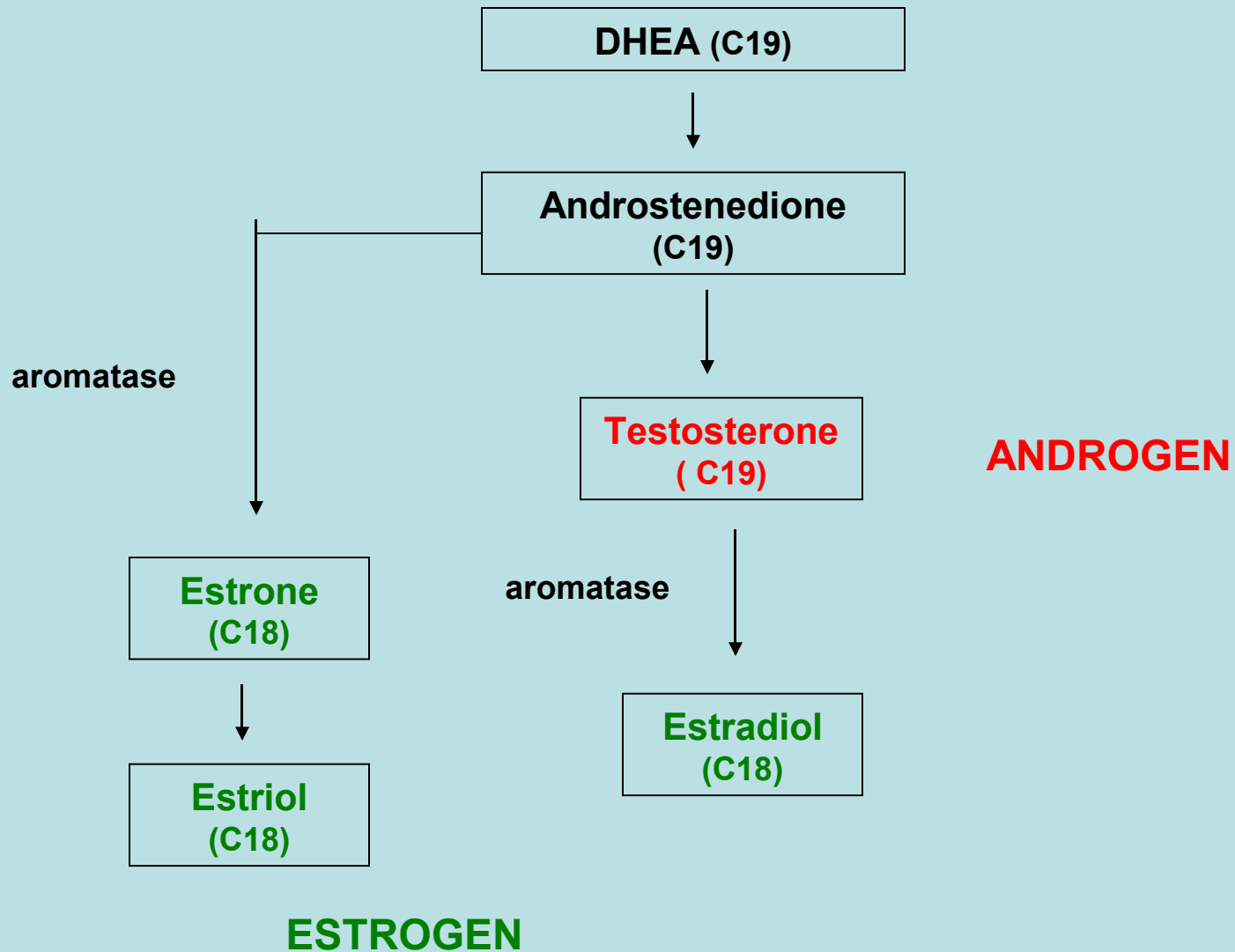
- Adrenal androgen was synthesized from cleavage of 2 carbon side chain of 17-OH-pregnenolone (C21) - forming 19 C adrenal androgen **dehydroepiandrosterone (DHEA)** – a weak androgen
- Synthesis occurred in zona reticulata of adrenal cortex

- DHEA converted to **androstenedione** – another weak adrenal androgen
- Androstenedione were reduced – forming **testosterone** – primarily in extra adrenal tissues
- Androstenedione can be converted into estrogen in the peripheral tissues – particularly in adipose tissue

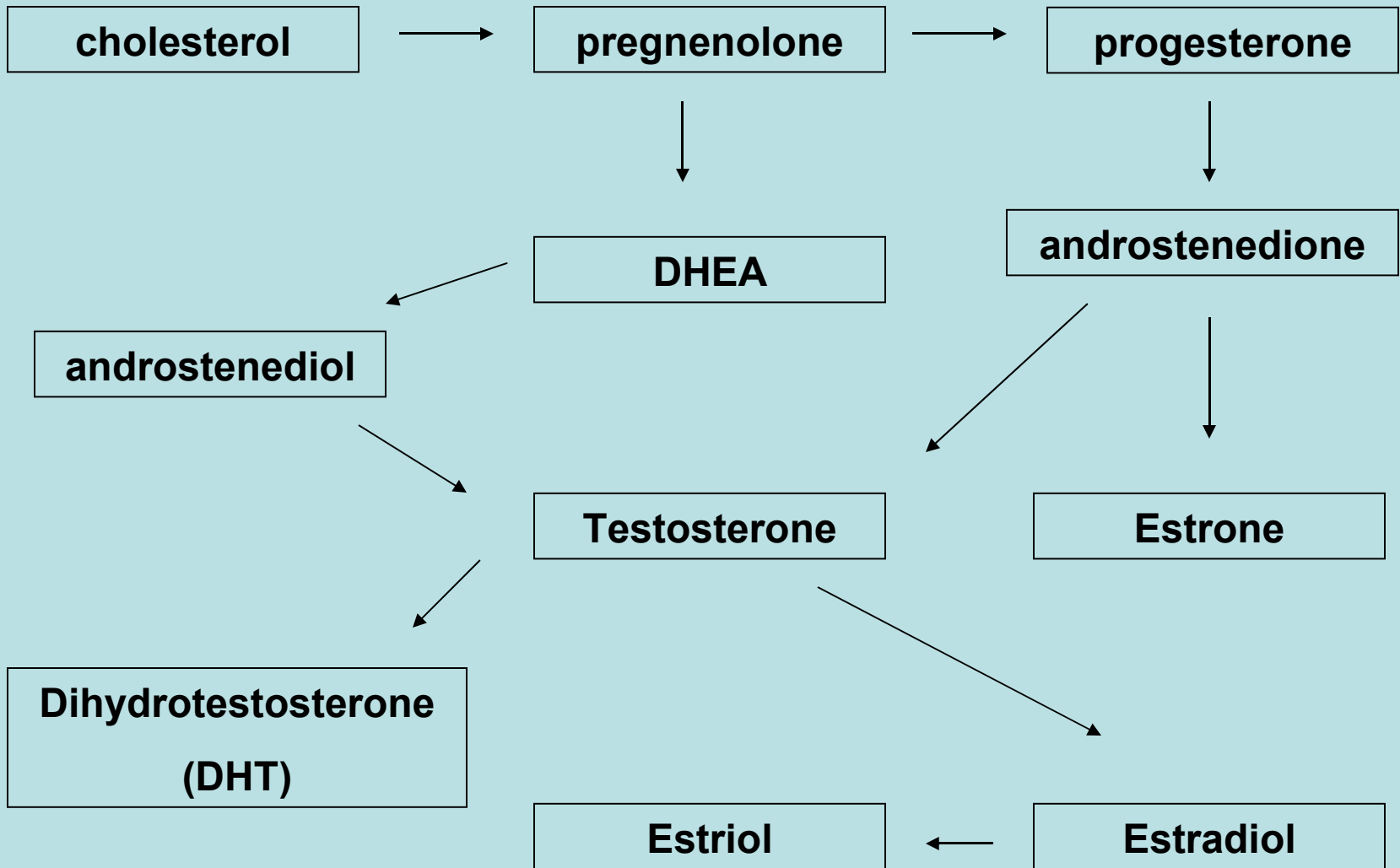


- Androgen – also synthesized in the theca cells at the periphery of ovarian follicle
- Androstenedione – produced by the adrenal cortex – about 3 mg/day – far less potent than testosterone – but the **major source of androgen activity in girls and women**

- **Boys and men** – produce small amount of estrogen (65 ug of estrone from androstenedione; 45 ug of estradiol from testosterone) – catalyzed by **aromatase**
- **In male** - a small quantity of estradiol is synthesized in testes, but most estrogen – produced in adipose tissue, liver, skin, brain
- Testosterone – precursor of 2 other hormones – **DHT & estradiol**



**Fig 3. Synthesis of estrogen from androgen**



**Fig 3. Major pathways for synthesis of gonadal steroids**

# TESTOSTERONE

- Synthesized in Leydig cells of the testes and ovary in response to LH
- The pathway of synthesis – similar to synthesis in adrenal cortex
- Cholesterol → pregnenolone → OH-pregnenolone → DHEA → androstenedione → testosterone
- In target cells: testosterone reduced into DiOH-testosterone (DHT)

# ESTROGEN & PROGESTERONE

- Estrogen – synthesized in the ovarian follicle & corpus luteum – stimulated by FSH
- Women of reproductive age – produce most of their estrogen in the granula cells of the ovarian follicle and the placenta during pregnancy
- Postmenopausal women still have estrone – derived from the adrenal androgen androstenedione

- In peripheral tissue - estrogens are synthesized from androgens
- In men – aromatisation of testosterone → estradiol - 80 % from this pathway
- In women – adrenal androgens were the main substrate for synthesis of estradiol – 50 % of estradiol in pregnant women produced from this pathway

- Synthesis of estrone from androstenedione – was the major pathway in post menopausal women
- **Activity of aromatase** – was found in adipose tissue, liver and skin
- Increased activity of aromatase – was found in “estrogenisation” in liver disease, aging and obesity