ANDROGEN INSUFFICIENCY IN WOMEN

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We all know…..

Estrogen Androgen

But do we also know there would be no estrogen without androgen

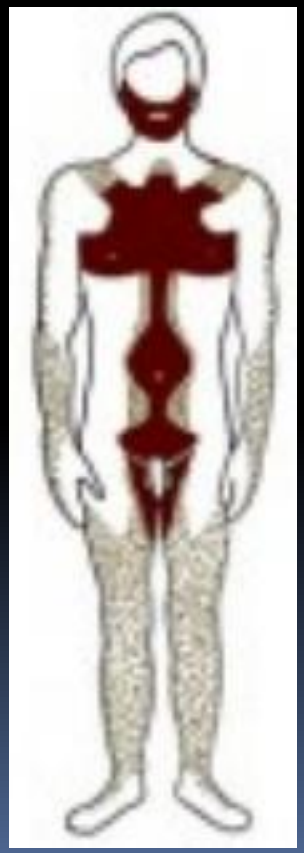
….when ‘ADAM’ tried to find a help-mate, none of the animals were satisfactory, and so God created a woman from his rib ‘EVE’.

Androgens are pre-cursors of estrogen

androgen

androgen → estrogen

estrogen



2 cell 2 gonadotropin theory

Pituitary LH

Pituitary FSH

theca interna

granulosa cells

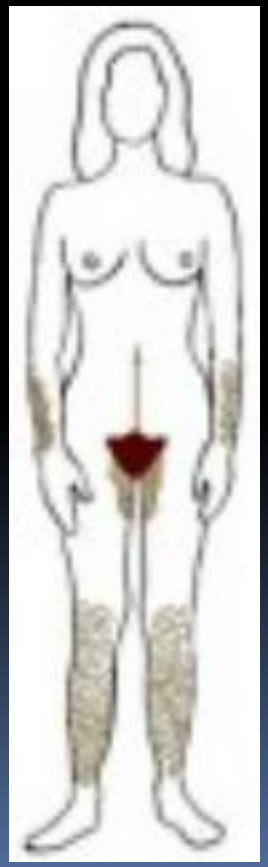
androgens

aromatase enzyme activity

(physiological levels act as substrate for androgens)

estrogen

estrogen microenvironment for oocyte growth



Females and androgen

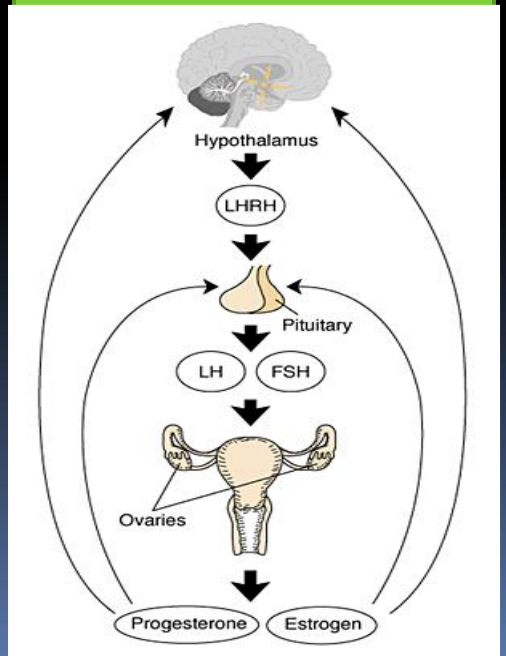
Androgen deficiency

- Free testosterone less than 1%

- **Poor ovulation**
- **Low libido**
- **Low body mass**
- **Chronic fatigue**

NORMAL ANDROGEN

Free testosterone 1 to 2%

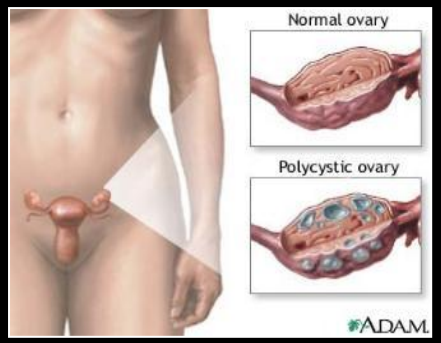


Androgen excess

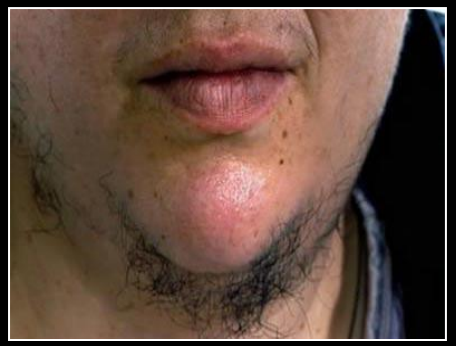
- Free testosterone more than 2 %

- **PCO**
- **Hirsutism**
- **Anovulation**
- **Hyperinsulinemia**

Androgen excess



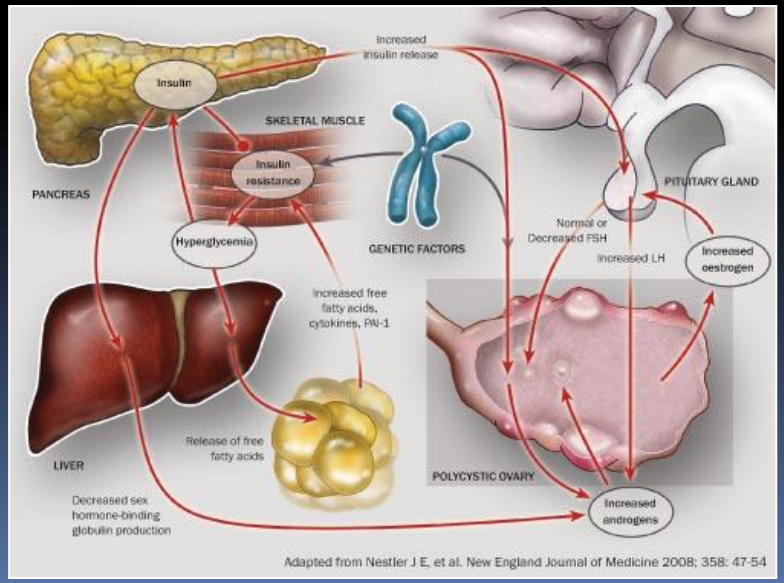
PCO

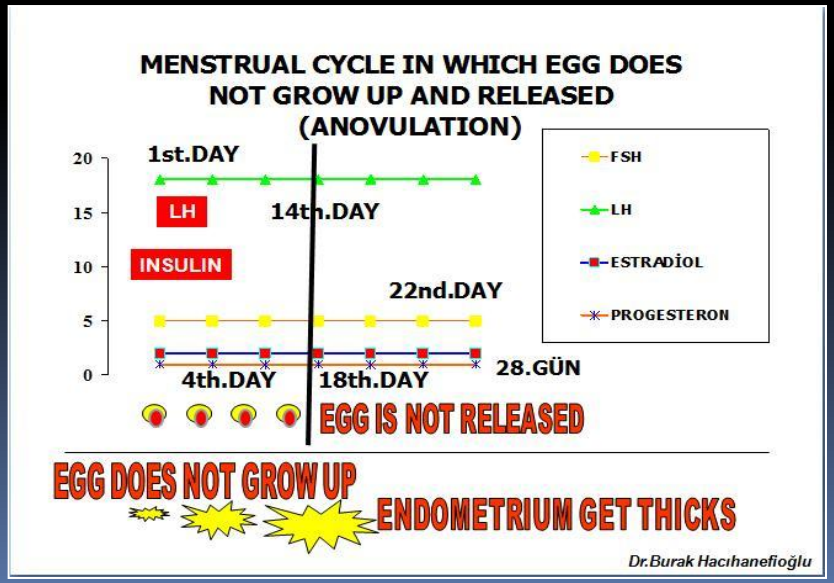


hirsute

PCO

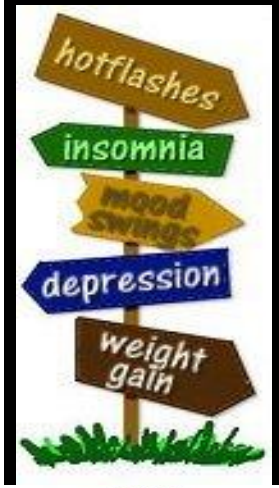
hyperinsulia

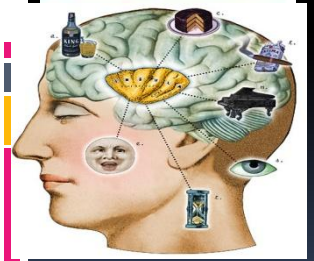




anovulation

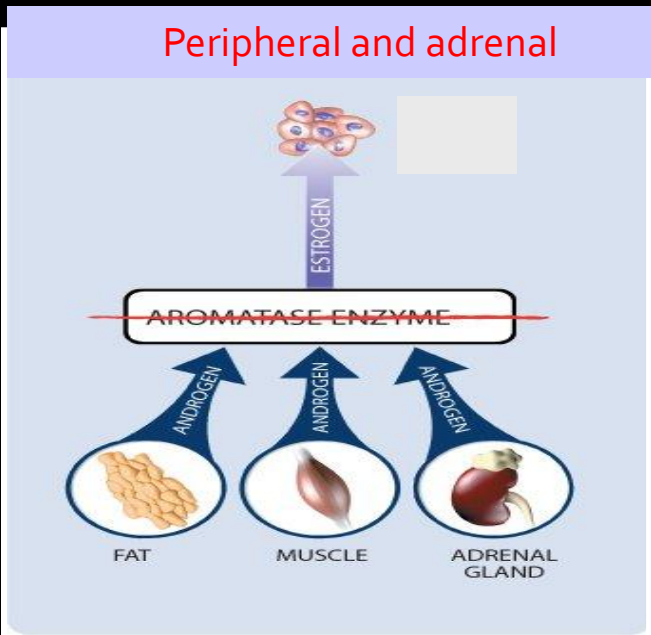
Androgen deficiency



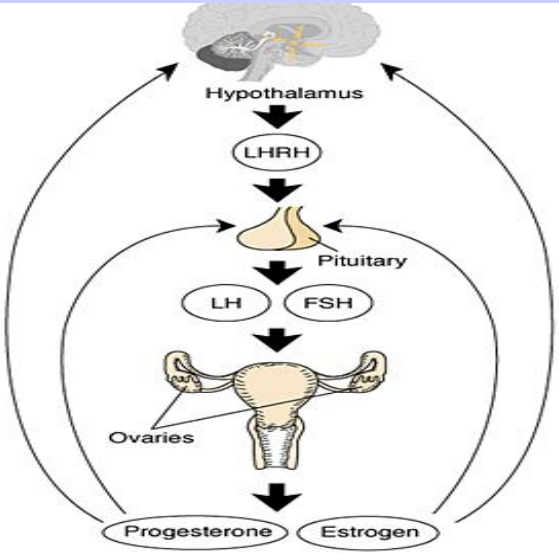


mood, energy & psychological well being

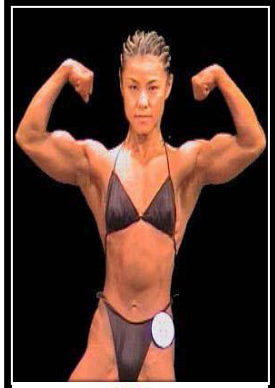
Peripheral and adrenal



H-P-O axis and Ovulation



Loss of libido



Bone density, muscle mass &adipose tissue

Definition of female androgen insufficiency syndrome (FAIS)

Female androgen insufficiency syndrome was redefined as a 'pattern of clinical features which occur in presence of decreased bio-available testosterone with normal estrogen status'.

Princeton consensus conference June 2001 at New Jersey

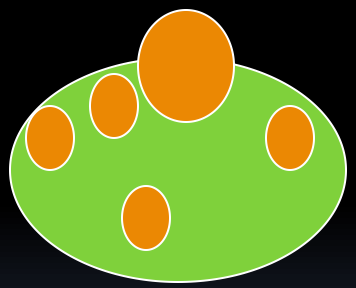
Criteria to diagnose female androgen insufficiency syndrome

- Clinical features:
  - Poor sense of well being, impaired sexual function (libido, receptivity and pleasure), persistent unexplained fatigue and bone loss
- Adequate estrogenization:
  - Absence of hot flushes or vaginal dryness with regular menses
  - or receiving estrogen replacement therapy
- Low free testosterone level:
  - Free T conc. at or below 25th percentile of normal for the age group

Androgen production

Three compartments

Ovary

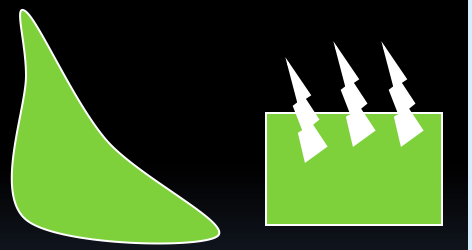


Stromal & thecal cells

Adrenal

Zona fasciculata & reticularis

Periphery & liver

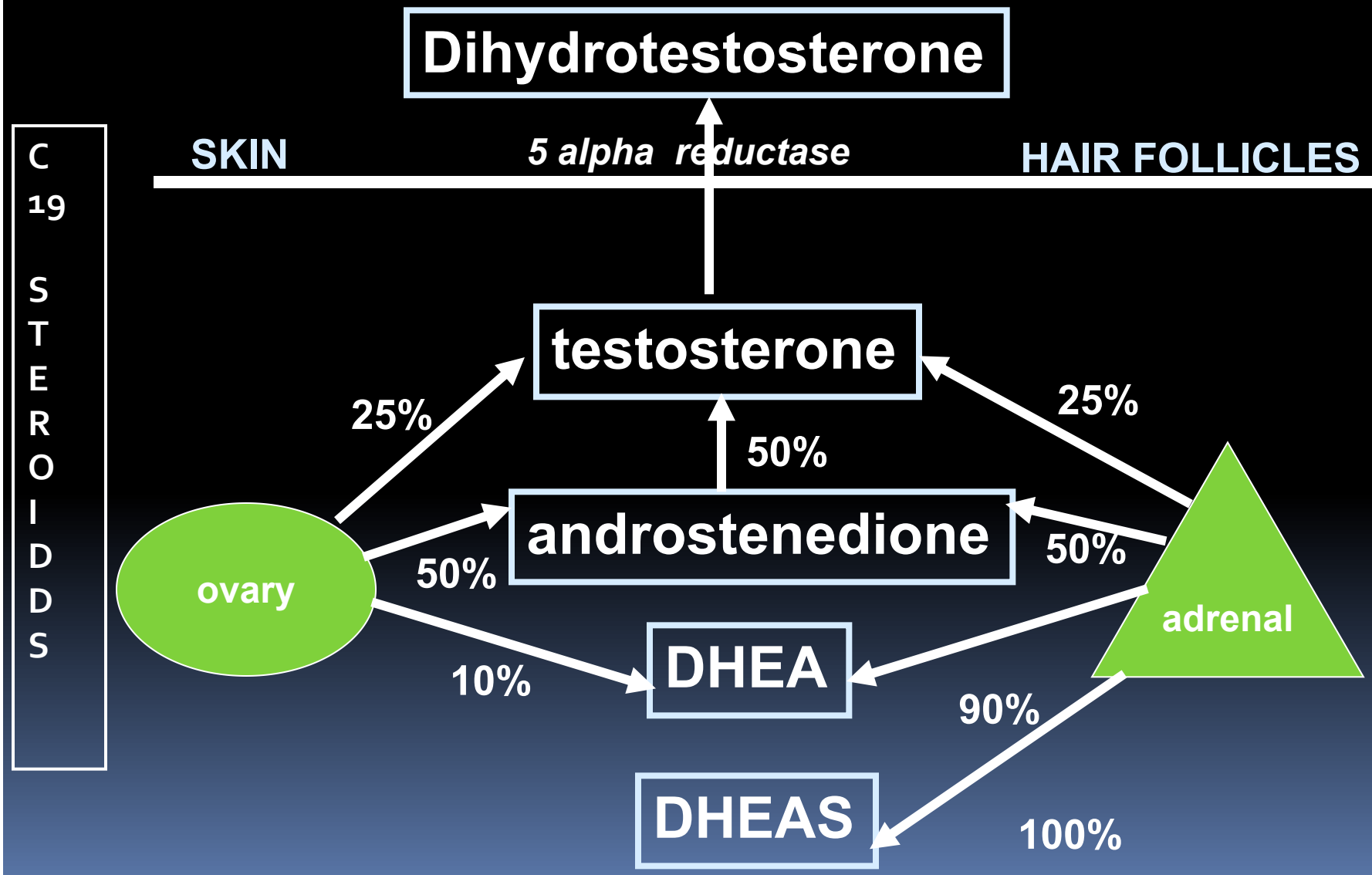


Skin, fat, blood pilosebaceous units

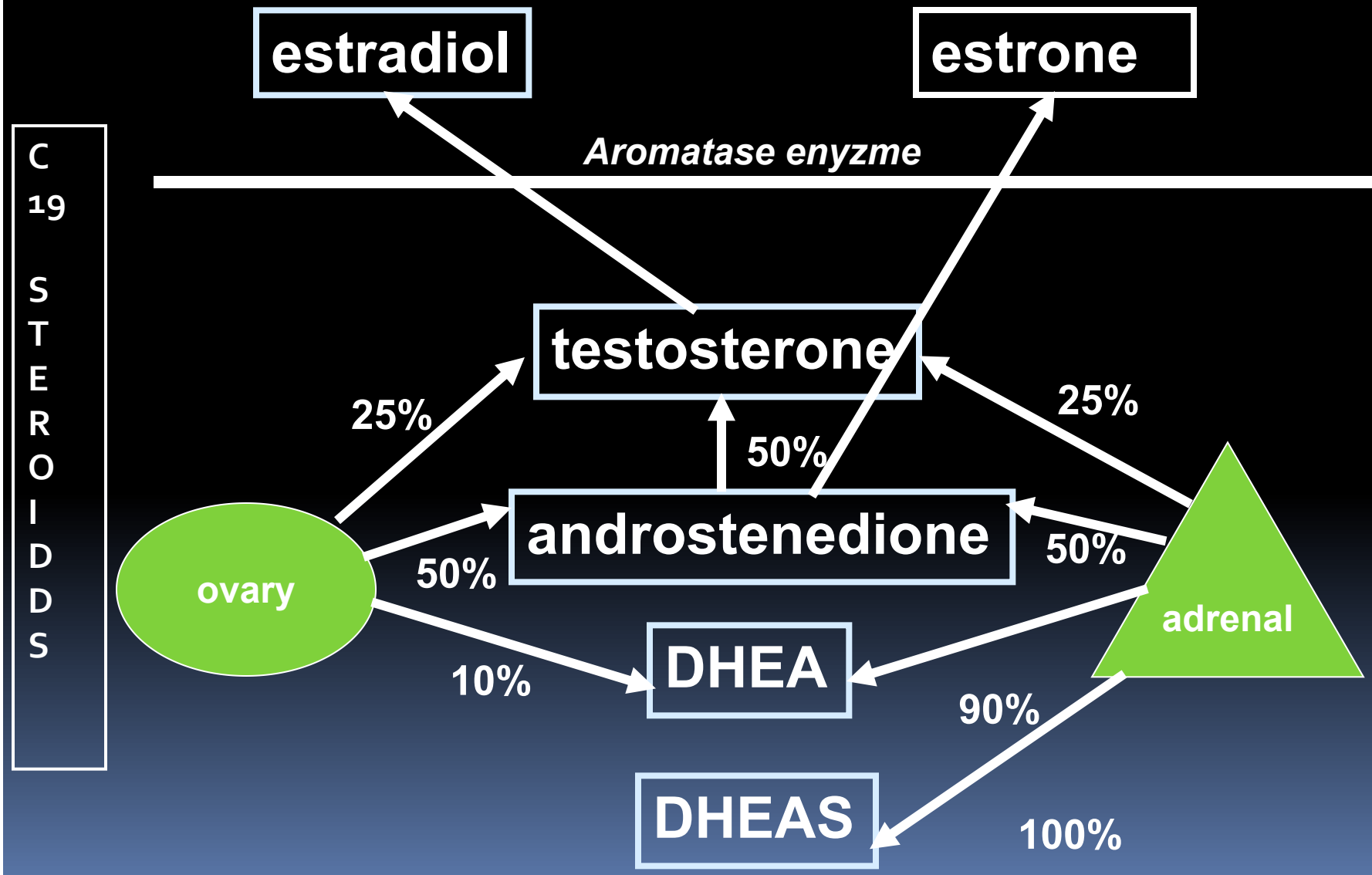
Target tissue: action of androgens

- CNS: hypothalamic pituitary limbic system
- Peripheral tissue: bone, breast, pilo-sebaceous unit, skeletal muscle, adipose tissue, gonads and genitals

Androgen production



Estrogen production



Role of androgen in women

- Development of reproductive function and hormonal homeostasis (immediate precursor of biosynthesis of estrogens):OVULATION
- Sexual desire, mood, & psychological well being: LIBIDO
- Bone density, muscle mass & strength, energy, adipose tissue distribution: FATIGUE

International Princeton consensus conference on androgen deficiency in women

- Estimation of androgen in women and pitfalls
- Causes of androgen deficiency
- Clinical sequel, diagnosis and management
- Research issues and priority

Fertil Steril 2002 77;660-665

Testosterone assay & measurement

Despite multiple sources of androgen production total androgen production best reflected by Testosterone (T)

- **Equilibrium dialysis** gold standard, though expensive and not readily available.
- **Free testosterone index** (total T/SHBG) correlates well with free T by equilibrium dialysis.
- **Analogue assays (RIA) for** Free T assays not well validated for women yet, unreliable and non-sensitive.

DHEAS assay & measurement

- DHEAS is most useful measure of adrenal androgen production in women
- Current assays for DHEAS are robust and reliable
- Not affected by diurnal variation
- DHEAS also synthesized in intracrine peripheral tissue more in menopausal state

Pitfalls in interpreting serum androgen levels:

- Testosterone action depends upon its intra-crine conversion and action in the same cell into:
  - DHT by 5alpha reductase

    or
  - estrogen by aromatase

- DHEAS also has intra-crine biosynthesis & actions without being spilled into peripheral circulation

- Androgen receptor sensitivity differs between individuals also in end organ response to circulating androgens

Androgen assays & measurement

When either Testosterone (total or free) is measured, concentration of circulating SHBG should be taken into account.

Increase in SHBG
Estrogen
Pregnancy
Hyperthyroidism

Decrease in SHBG
Androgens
Progestins
Insulin and IGF -1
Growth hormone
corticosteroids

Testosterone values to be obtained in morning hours (has cicardian rhythm) and in middle third of menstrual cycles

Causes of androgen insufficiency

- **Ovarian**
  - Surgical, radiological or chemotherapeutic menopause
- **Endocrine**
  - Adrenal insufficiency
  - Pan hypo-pituitarism
  - hyperthyroidism
- **Drug related**
  - OCP, oral HRT, anti androgenic agents, corticosteroids
  - excessive thyroxine replacement
- **Disease states**
  - HIV wasting syndrome, SLE, Rheumatoid arthritis, anorexia nervosa

Clinical sequel, diagnosis, and management of FAIS

- Poor ovulatory performance with normal basal hormones
- Lack of sexual desire
- Chronic fatigue

Ovulatory performance in primates

Granulosa cell stimulation by FSH is an androgen modulated process (primate ovary)

Hillier and De Zwart,1981; Harlow et al.,1986

- Testosterone augments follicular FSH receptor expression and sensitivity in granulosa cells
  - Weil et al., 1998, 1999
- Promotes initiation of primordial follicle growth
- Increases the cohort of pre antral and small antral follicles .

Vendola et al., 1999 and 1998

Ovulatory performance in humans

Studies suggest androgen pretreatment may amplify FSH effects on the human ovary

- Testosterone (dermal patches or parenteral)
- De-hydro-epiandrosterone (orally)
- Letrozole (orally)

Unexpected poor responder(UPR)

- Age less than 41
- Normal basal FSH
- No apparent reason for repeated low response to aggressive stimulation protocols in ART cycle

Fasouliotis et al., 2000 J Assist Reprod Genet 17,357-373
Klinkert et al., 2004Fertil Steril 81,1247-1253

USG Observation of poor response in UPR in clinical setting

- Population of follicles ready to be recruited in initial follicular phase of natural cycle is lower in such patients compared to normal responders

  Pellicer et al.,1998 Fertil Steril 70, 671-675

- Pre-treatment with testosterone (age<41, FSH<10)
  - 25 patients proven poor responders (2 cycles consecutively cancelled due to poor response **AFC 5.56+_ 0.49**
  - 20 patients completed IVF cycle with good response after testosterone pretreatment **AFC 12.76 +_1.30 (P<0.0001)**

  Balasch et al.,2006 Hum Rep 21,1884-1893

Androgen pre-treatment in poor responders

Huges et al., 2004 Fertil Steril 82 suppl.2 S123

- Poor responders by previous cycles <5OR
- High basal hormones **FSH<20miu**
- Testosterone **15mg/d for 15 days** prior to stimulation
- No difference in OR and PR

Balasch et al., 2006 Hum Rep 21,1884-1893

- Poor responders 2 previous IVF cycles cancelled <3OR
- Normal basal hormones **FSH<10miu**
- Testosterone **12mg/day for 5 days** prior to stimulation
- OR=80% and PR30%

Androgen pre-treatment in poor responders

Dehydroepiandrosterone (DHEA) oral 80 mg/d for 2 months and ovarian stimulation while still on DHEA
Better response in terms of OR and PR
(FSH < 20 age <41 poor responder)
Casson et al.,2000 Hum Rep 15 2129-2132

Letrozole 2.5 mg/d x 5 days with gonadotropins induces temporary accumulation of intraovarian androgens and improves IVF outcome in low responders (FSH<12IU/L, <5 OR in previous cycle)
Mitwally and Casper, 2002 Fertil Steril 77,776-780:
Garcia-Velasco et al.,2005 Fertil Steril 84,82-87 A pilot study

The daily dose, timing and duration of androgen supplementation may be critical to adequately stimulate folliculogenesis

Concentration dependant interaction between FSH and testosterone seem to exist

Ability of testosterone to interfere with FSH stimulated ovarian function may be overridden by elevated levels of FSH

Zeleznik et al., 2004

Chronic administration of high dose of androgen is antagonistic to gonadotropin stimulated ovarian function in primates.

Zeleznik et al., 2004 J Clin Endocrinol Metab 89,860-866

Threshold effect of androgen for follicular function

- Agonist action of androgen at lower levels
- Antagonist action at higher levels

Balasch et al., 2006 Hum Rep 21,1884-1893

Evidence for other beneficial effects of testosterone therapy

There is evidence of relationship between androgen deficiency and mood and sense of well being

Improvement is seen with **testosterone therapy** in pre and post menopausal women

DHEA has shown no beneficial effect on mood or well being

Effect of testosterone therapy on mood and well being:

Testosterone patches 300 mcg/d > 12 weeks in surgical menopause; significant improvement in 'Psychological general well being index' scores *Shifren et al., 2000*

Natural menopause testosterone therapy positive effects *Brincat et al.,1984; Montgomery et al., 1987*

Addition of I/M testosterone or testosterone implants (50 mg) to estrogen replacement in surgical or natural menopause: improved general well being
Shifren et al., 1988 1987

Effect of DHEA therapy on mood and well being:

- DHEA no evidence of improvement on mood and well being in elderly men or women as well as in women with hypo-piuitarism; Oral50 mg/day or transdermal cream 10%

  Flynn et al 1999; Johannsson et al

- Beneficial effect in women with adrenal deficiency *Arlt et al.,1999*

Androgens and sexual function

Low Testosterone closely related to loss of sexual desire. T restores libido in post menopausal women

- Following bilateral opherectomy 50% reduction in circulating testosterone Judd et al., 1994. After opherectomy worsening of sexual life compared to natural menopause Nathorst Boos et al.,1992
- ERT in post menopausal women improves vasomotor symptoms, vaginal dryness and general well being but no effect on low libido **Utian, 1972; Campbell et al.,1997**

Other beneficial effects of androgen therapy

- Addition of testosterone to standard estrogen therapy helps women with poorly controlled hot flushes
- Vaginal blood flow improves sexual arousal
- Bone health positively affected by addition of androgens to standard HRT.

  Oral estrogen replacement causes high SHBG with low testosterone associated with loss of vertebral height

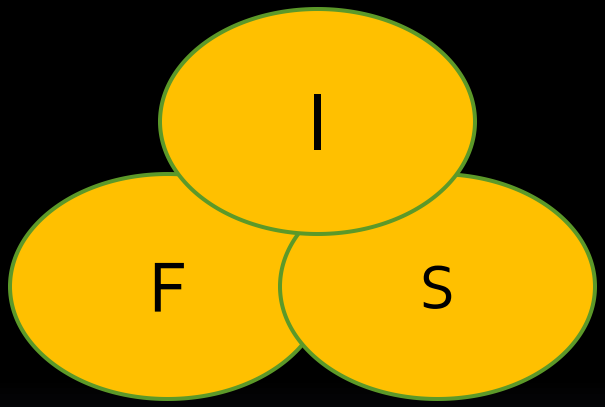
Potential risks of testosterone replacement in women

- Hirsutism and androgenization
- Hepatic dysfunction and altered lipid metabolism with certain oral preparations
- Breast and ovarian malignancy as androgens are converted to estrogens potentiating their effects on these organs
- Virilization of female fetus in reproductive age

Research needs and priorities

- Define normal androgen levels in different decades of life
- Development of reliable assays to determine lower ranges of androgen
- Identify stable biological markers for androgen insufficiency
- Evaluate safety, efficacy and appropriate dosage of androgen replacement as well as clinical markers to predict response to therapy

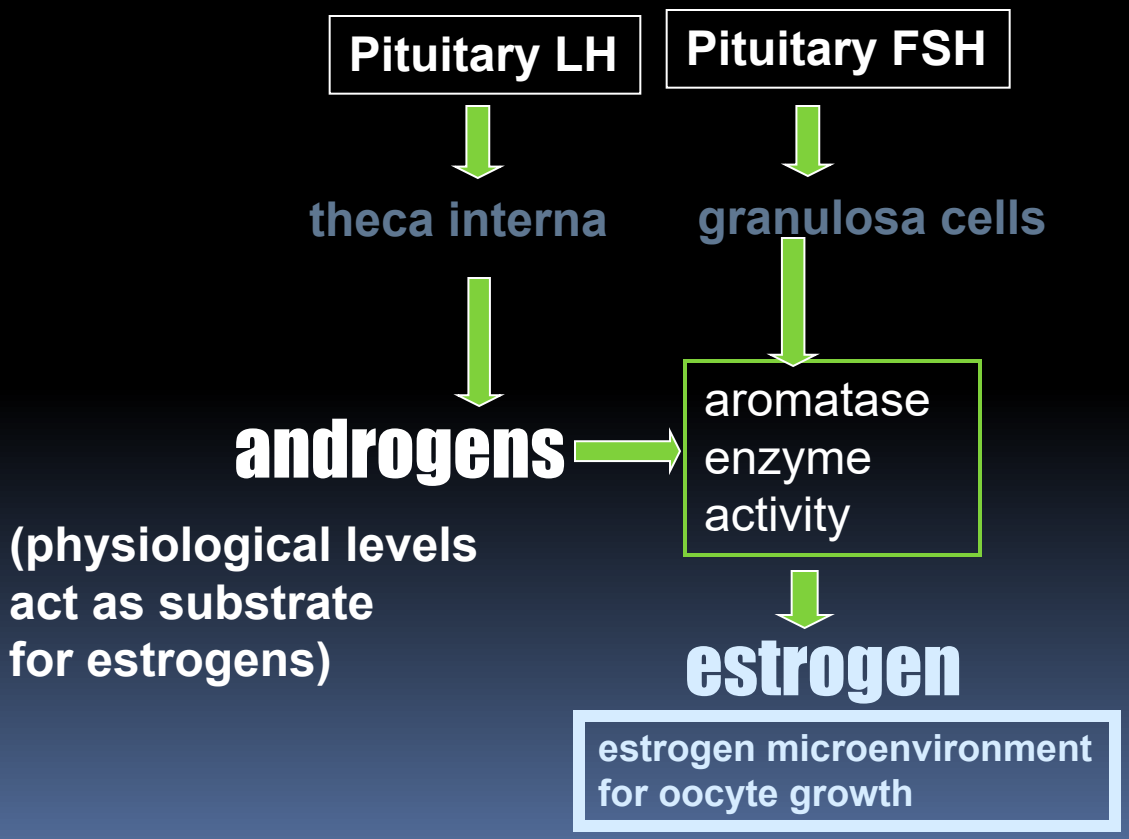
With best wishes



Indian Fertility Society

The two cell two gonadotropin theory

androgen → estrogen



Explanation of poor response in UPR in research setting

- Interference in FSH action due to low and higher mol. wt proteins
- Presence of antibodies against granulosa cells
- Defective angiogenesis
- Autocrine or paracrine alterations leading to decreased intra-ovarian peptides
- FSH receptor pleomorphism

Pellicer et al.,1998 Fertil Steril 70, 671-675:

Fasouliotis et al.,2000 J Assist Reprod Genet 17, 357-373: Klinkert et al.,2004 Fertil Steril 81,1247-1253Low diffusion of exogenous gonadotropins

Causes of chronic fatigue

- Major life stress or relationship conflicts
- Thyroid disease (hypo or hyper)
- Major metabolic nutritional disorders such as iron Vit. B12,or Vit. D deficiency
- Chronic fatigue eg. Lyme disease, chronic fatigue syndrome
- Psychiatric depressive disorder

Androgen insufficiency may coexist with any or all of the above condition or may present alone as chronic fatigue

Androgen pre-treatment in poor responders

- Effects of transdermal testosterone application for 15 to 20 days before stimulation with FSH in poor responders undergoing ART in a prospective, randomized, double blind study
  - FSH> 12 IU/l, E2 >70pg/ml, Inhibin B<45pg/ml

- Conclusion: no significant beneficial effects of androgen administration on the ovarian response to FSH could be demonstrated.

  Massin et al., Hum.Reprod 2004,21 1204-1211