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Hyperandrogenism of Ovarian Non-tumorous Origin

Atanas Shterev

Initial Statistics

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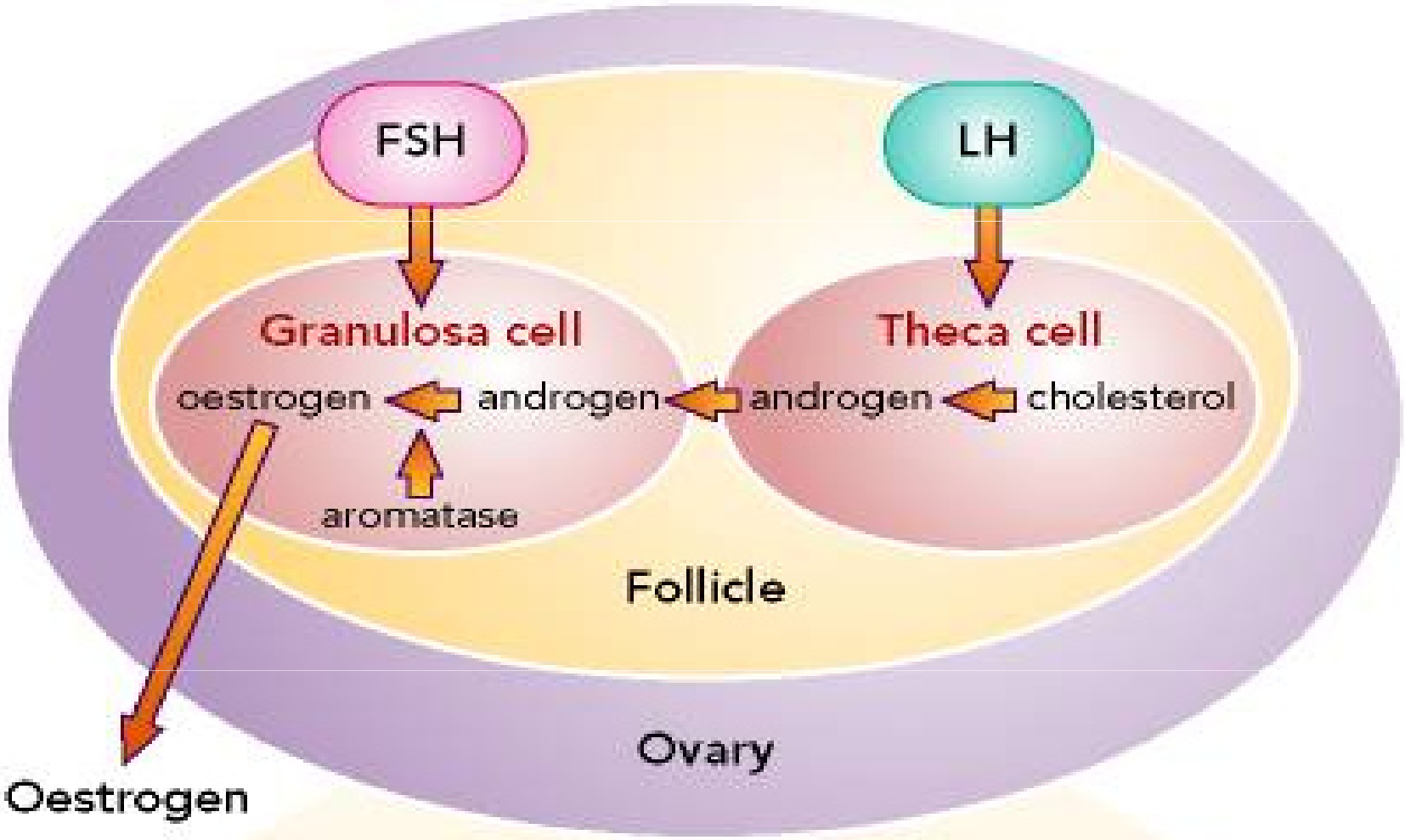
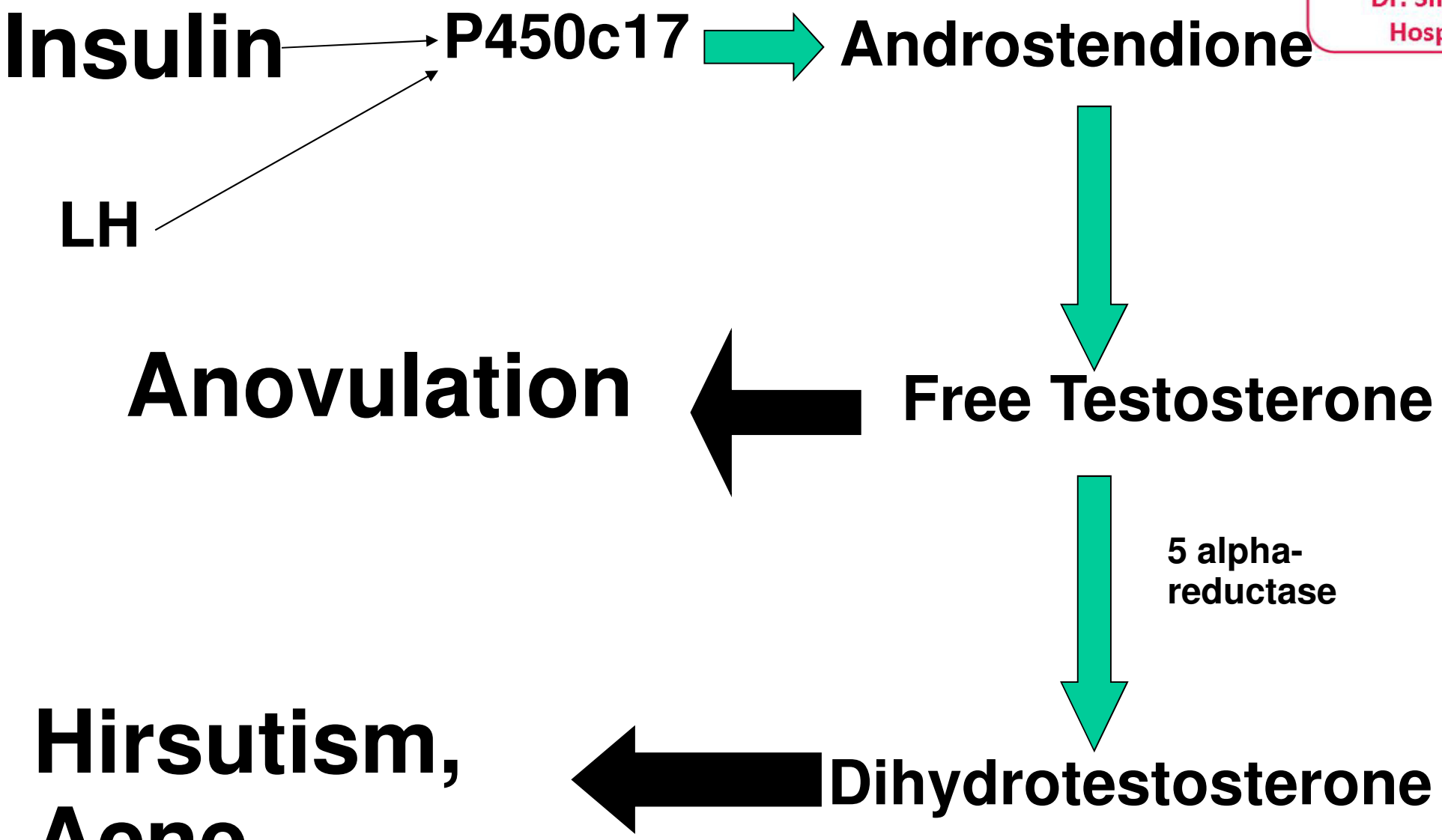
17-33% of the “normal” population have polycystic ovaries

- Botsis et al, Ultrasound Obstet Gynecol 1995;6:182
- Clayton et al, Clin Endocinol Oxf 1992;37:127
- Cresswell et al, Lancet 1997;350:1131
- Farquhar et al, Aust N Z J O & G 1994; 34:67
- Koivunen et al, Acta O&G Scand 1999; 78:137
- Michelmore et al, 1999 Clin Endocrinol 1999; 51:779
- Polson et al, Lancet 1988; 1:870
- Tayob et al, BR J Family Planning 1990; 16:94

Hormonal regulation of steroid hormones



Androgens produced by LH-stimulated **theca cells** are the main substrate for FSH-induced oestrogen synthesis in the **granulosa cells** by FSH.



Evaluation of hirsutism - Ferriman-Gallwey Modified Score

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Face	0 pt. Lanugo hair 1 pt. Single hairs 2 pts. Scattered hairs 3 pts. Beard of rarely located hairs 4 pts. Shaped thick beard
Thorax	0 pt. Lanugo hair 1 pt. Single hairs around areoles 2 pts. Hairs along middle line 3 pts. Single hairs of limited concentration plus scattered hairs of limited concentration 4 pts. Total hairs
Abdomen	0 pt. Lanugo hair 1 pt. Single hairs along the median line 2 pts. Strip of hairs along the median line 3 pts. Band of hairs along the median line 4 pts. Masculine type of hair in the shape of rhomb
Proximal part of limbs	0 pt. Lanugo hairs 1 pt. Single hairs – up to ¼ of the surface 2 pts. Expressed growth, covering ¾ of the surface 3 pts. Complete hairs of rarely located hairs 4 pts. Complete hairs of thickly located hairs
Spine	0 pt. Lanugo hairs 1 pt. Shaft of hairs in the area of the sacrum 2 pts. Strengthening of hairs in lateral direction 3 pts. Hairs on ¾ of the surface 4 pts. Complete hairs

Common data

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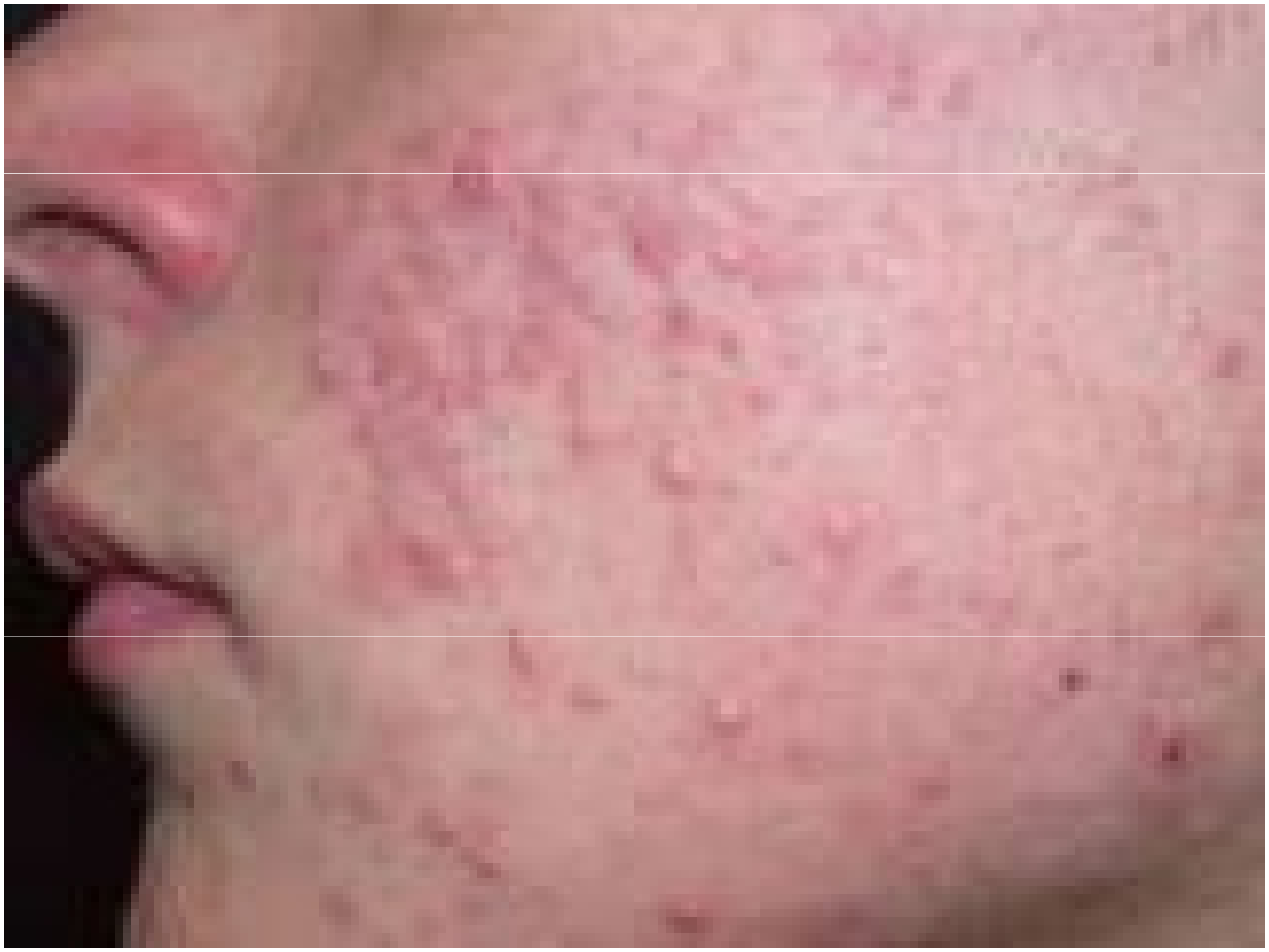
Two essential intrafollicular hormones regulate hair cycles: dihydrotestosterone and estrone.

Dihydrotestosterone reduces adenylcyclase activity so that the follicle turns into catagen and the hair becomes telogen.

Today, it is safe to assume that male androgenetic alopecia is associated with an **increase in 5-alpha reductase activity** which, genetically, leads to higher levels of dihydrotestosterone but this has been studied mainly, if not exclusively, in males.

Estrone increases adenylcyclase activity, and thus maintains the mitoses of the matrix, and the duration of the anagen. It also activates the stem cells in the early stages of the anagen phase.

Acne vulgaris



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Assumption

It is reasonable to assume that the common denominator in the pathophysiology of **acne, hirsutism , alopecia and anovulation** is the altered concentrations of the androgens - **hyperandrogenism**

Known pathophysiological states of hyperandrogenism

Ovarian Hyperandrogenemia from tumor origin	**Adrenal** Hyperandrogenemia from tumor origin	**Adrenal** Hyperandrogenemia from non- tumor origin/ Various forms of AG syndrome	**Increased androgen** sensibility with normal androgenic levels/ in analogy with lacking androgenic receptivity	**Ovarian** Hyperandrogenemia of non-tumor origin /**HONTO**/

Clinical Hyperandrogenism

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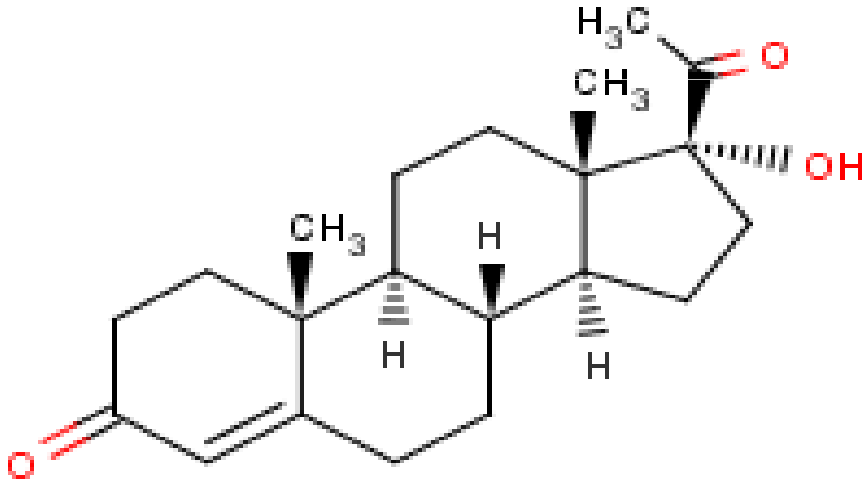

Ovarian and non-ovarian forms with innate adrenal cortical hyperplasia and tumors of the adrenal glands and the ovaries. The increased 17-alpha hydroxyprogesterone is accompanied with the PCO symptoms but it is a disease with **clearly established genesis and therapeutic options**.

GENETIC BACKGROUND

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Researchers have identified a gene that appears to determine cyclical hair loss in mice and believe it may also be responsible for hair loss, or alopecia, in people.

In a report published in the Proceedings of the National Academy of Sciences, the scientists described how they generated a line of **mice** that were lacking in the **Sox21 gene.**

"The mice started to lose their fur from postnatal day 11, beginning at the head and progressing toward the tail region of the back," they wrote.

Between day 20 and day 25, these mice eventually lost all of their body hair, including the whiskers. Intriguingly, new hair re-growth was initiated a few days later but was followed by renewed hair loss."

The cyclical alopecia continued for more than two years and the researchers observed that the mutant mice had enlarged oil-secreting sebaceous glands around the hair follicle and a thickened layer of skin cells during periods of hair loss.

Journal of Human Genetics (2005) ***50,*** *534–537; doi:10.1007/s10038-005-0289-x*

GENETIC BACKGROUND – References

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Sanders EB, Aston CE, Ferrell RE, Witchel SF. Inter- and intrafamilial variability in premature pubarche and polycystic ovary syndrome. Fertility and Sterility - September 2002 (Vol. 78, Issue 3, Pages 473-478).

Batzis et al. Polymorphism T→C (−34 bp) of gene CYP17 promoter in Greek patients with polycystic ovary syndrome. Fertility and Sterility, 1999, 431-435.

Xiaomiao Zhao, Renmin Ni, Lin Li, Yaqin Mo, Jia Huang, Meifeng Huang, Ricardo Azziz, Dongzi Yang. Defining hirsutism in Chinese women: a cross-sectional study. Fertility and Sterility, 2011 Vol. 96, Issue 3, Pages 792-796

PCOS

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The term polycystic ovari syndrome (PCOS) was introduced and universally accepted during the 1970-80s mostly through the publication of Yen, S.S.C. in Clin. Endocrinology. However, this term is broad and includes all known diseases such as tumor forms of hyperandogenemia, Cushing syndrome, acromegalia, hyperthyreoidismus etc. This definition is the reason for many misunderstandings, hyperdiagnostics, and unduly treatment, surgery included.

Yen, S.S.C, Chaney, C.,Judd, H. L.,The polycystic ovary syndrome, Clin. endocrinol., 12:177, 1980

Yen, S.S.C. et al (1976) *Functional aberations of the hypothalamic-pituitary system in polycystic ovary syndrome: a consideration of the pathogenesis,* The Endocrine function of the human ovary, p. 519

Controversy around the definition of PCOS continues

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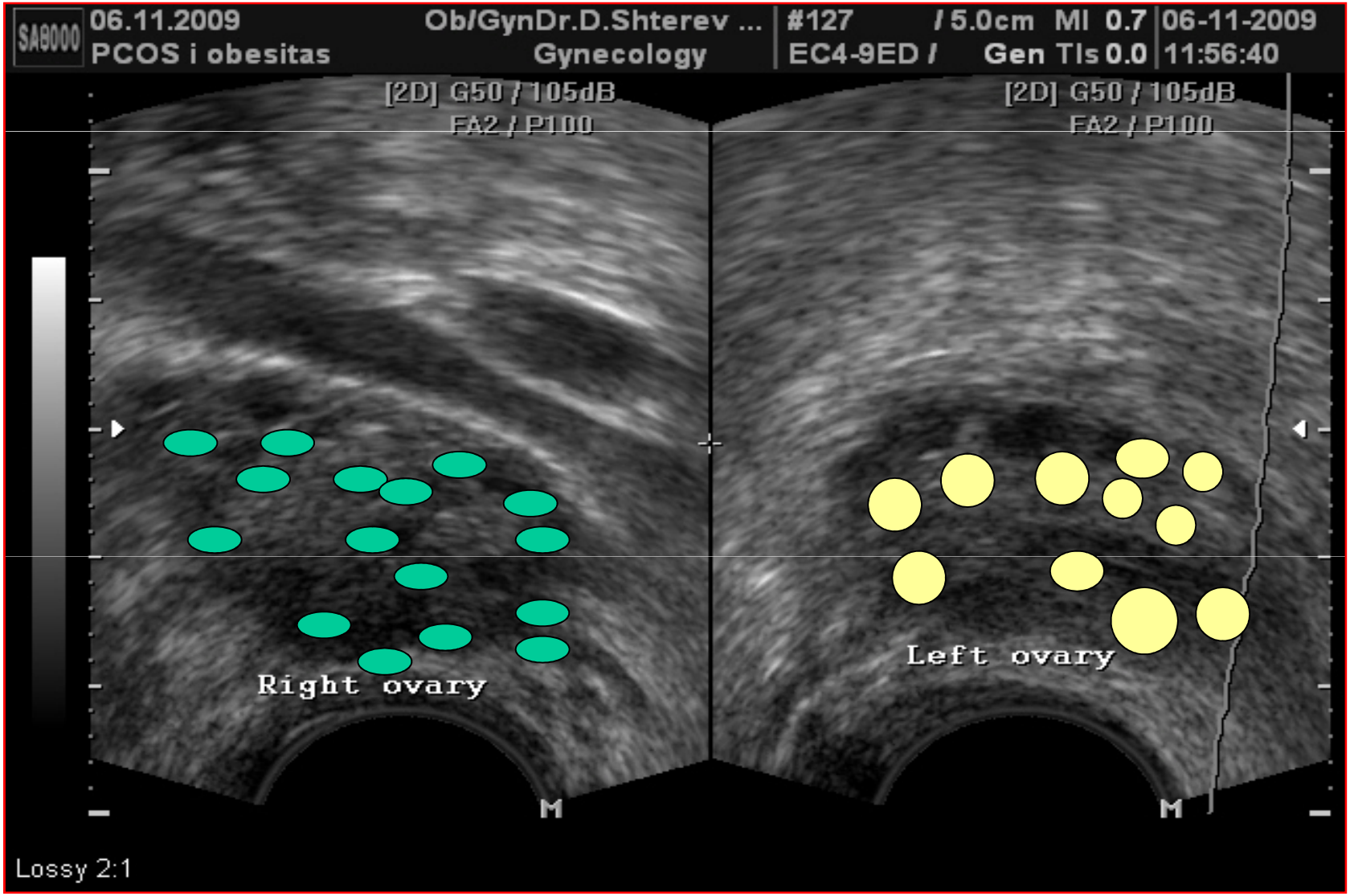

US scan of polycystic ovary

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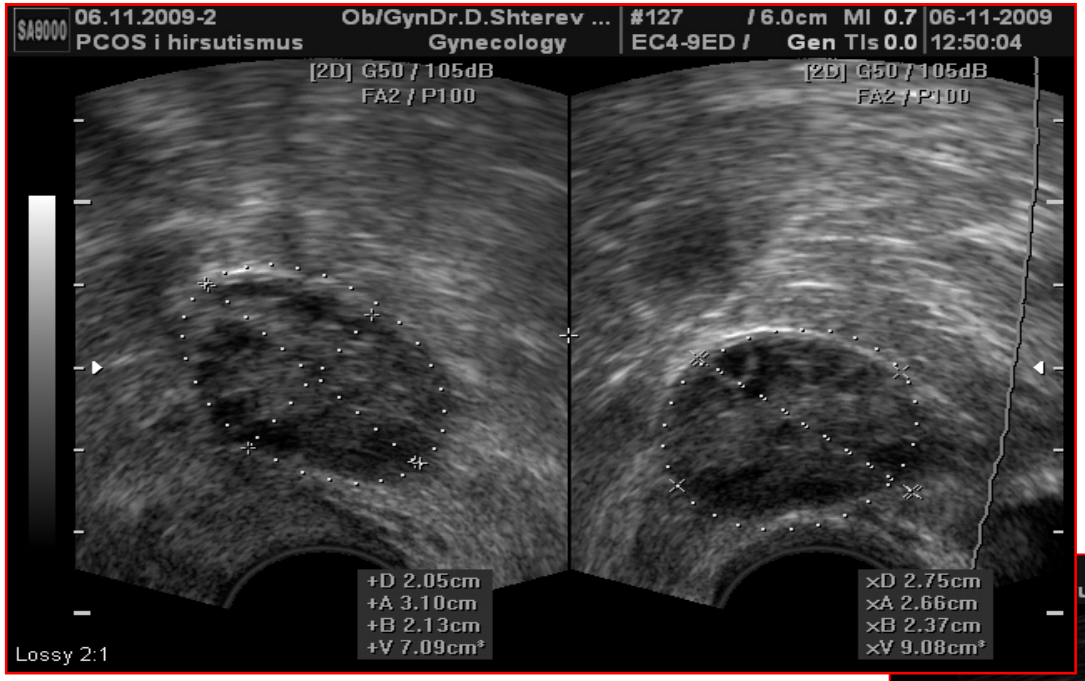

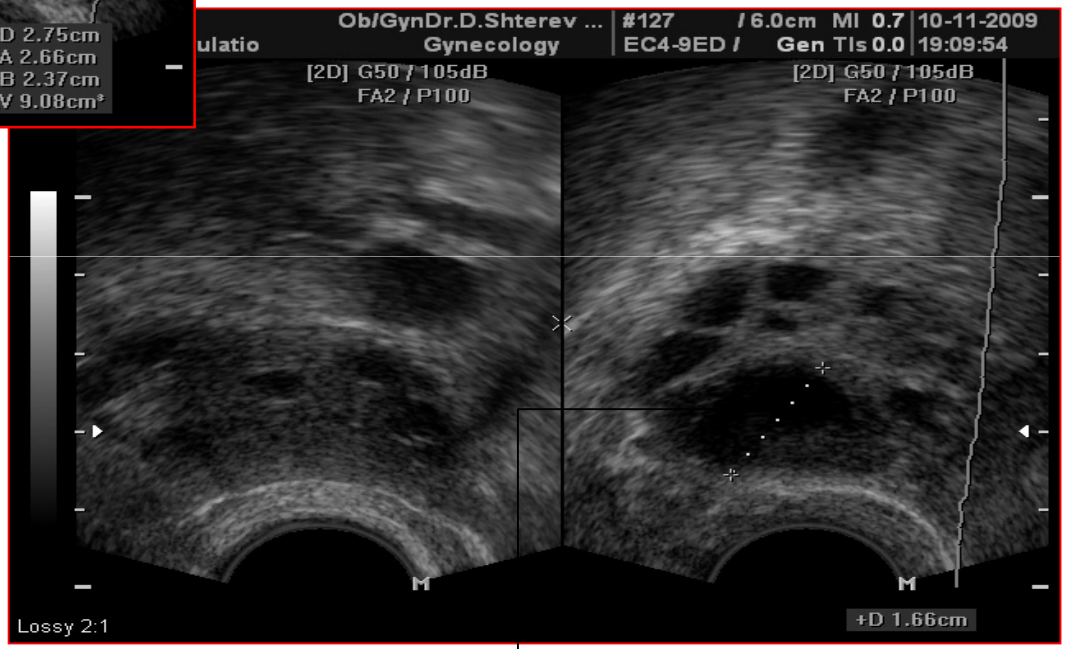

Ovulatory follicul

Clinical Hyperandrogenism

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Hyperandrogenism must be considered in any girl with premature pubarche, unusual acne, hirsutism, or androgenetic alopecia. An association with menstrual irregularity or obesity should raise the index of suspicion.

The most common causes of hyperandrogenism presenting in a teenage girl are functional ovarian hyperandrogenism, one manifestation of which is polycystic ovary **symptom**, and functional adrenal hyperandrogenism, which usually seems to be due to an exaggeration of adrenarche. The plasma-free testosterone is a more sensitive indicator of hyperandrogenism than is the total testosterone concentration.

Clinical Hyperandrogenism

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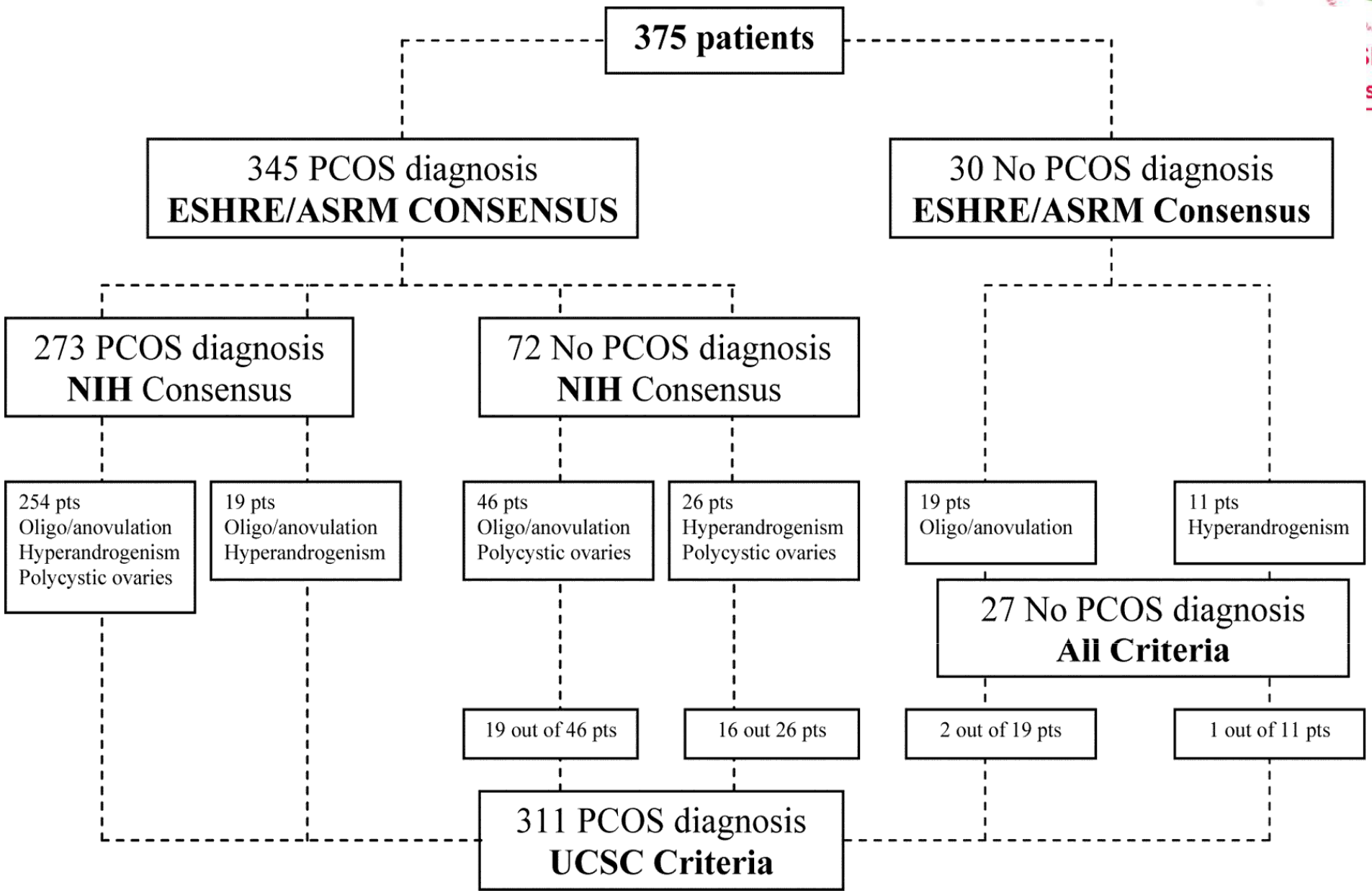
Carmina et al (2006) have reevaluated the data in the records concerning the clinical evaluation of hyperandrogenism , body weight and height, testosterone (T), free T, dehydroepiandrosterone sulfate, 17-hydroxyprogesterone, progesterone and pelvic sonography of 950 patients. The prevalence of androgen excess disorders was:

- PCOS, 72.1% (classic anovulatory patients, 56.6%; mild ovulatory patients, 15.5%),
- idiopathic hyperandrogenism, 15.8%;
- idiopathic hirsutism, 7.6%;
- 21-hydroxylase-deficient nonclassic adrenal hyperplasia, 4.3%;
- androgen-secreting tumors, 0.2%. Compared with other androgen excess disorders, patients with PCOS had increased body weight whereas non-classic adrenal hyperplasia patients were younger and more hirsute and had higher serum levels of T, free T, and 17-hydroxyprogesterone.

The studies of Carmina et al (2006), Belosi et al (2006), and Rosenfield et al (1993) reveal convincingly that **the major problem in these patients is the existing hyperandrogenism** although with different causes but the polycystic ovarian syndrome.



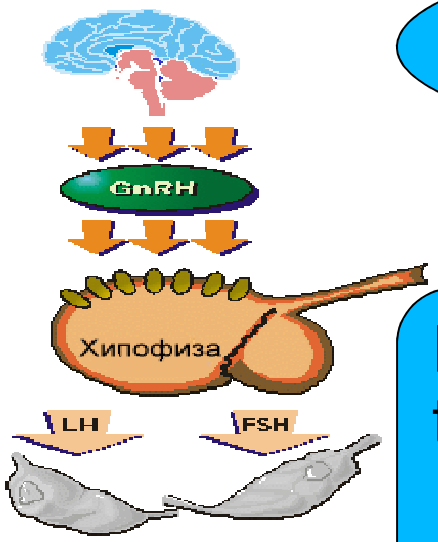
Belosi C et al. Hum. Reprod. 2006;21:3108 -3115

Hyperandrogenism

Regulation

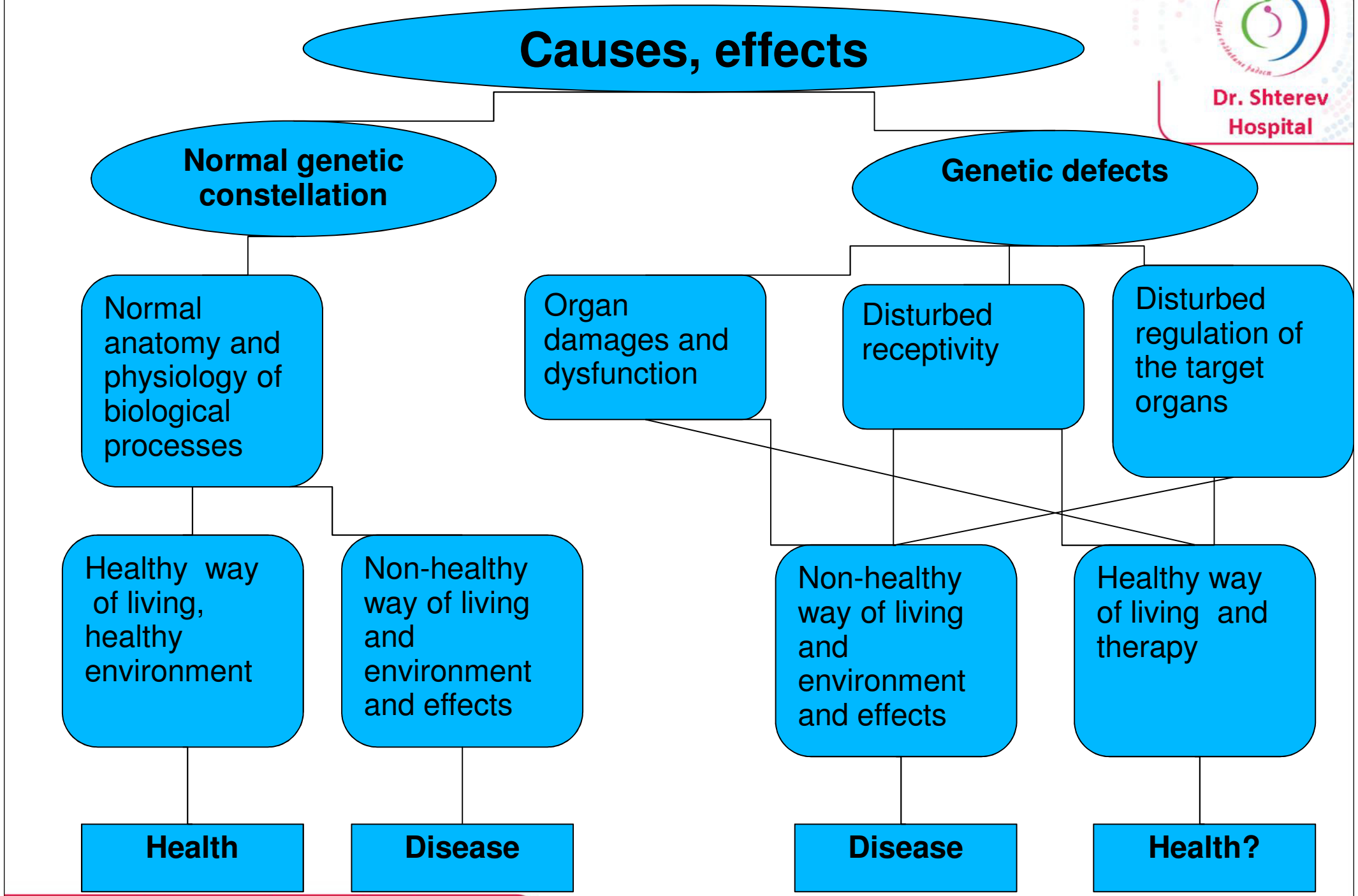
Adrenal

- Hormonal tumors
- Various forms of innate adrenal cortical hyperplasia



Ovarian

- Hormonal tumors
- HONTO
  - Primary Hyperandrogenism
  - Secondary Hyperandrogenism
  - Tertiary Hyperandrogenism



HONTO

The key to effective therapy of each disease is the valid diagnosis and the pursuit to recognize the pathophysiological mechanism of the disease. As early as the 60-es of the last century our teacher S.I.Докumov proposed the term HONTO (**hyperandrogenemia ovarialis from non-tumor origin**) which we currently use instead of the widely used term PCOS (polycystic ovari syndrome).

Nevertheless the level of the disturbances in HONTO – hypothalamic, pituitary or ovarian, the phenomenon of the policystic ovari can not be a unifying diagnostic criterion, because it is just a symptom of the disturbed regulation of HPO axis, which quite easily influenced by treatment and can be observed with tens of well defined diseases.

References

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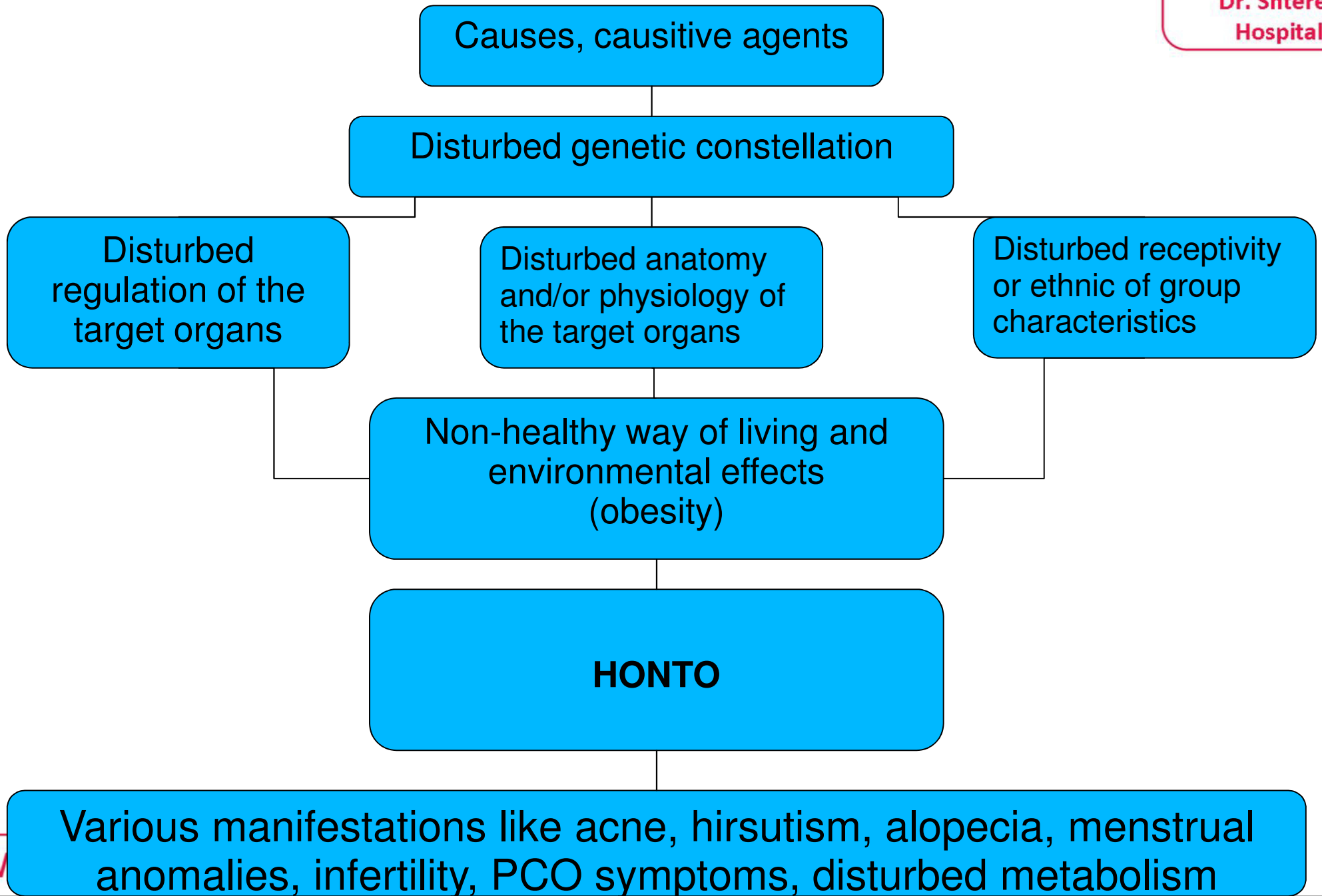
-Valkov, I.M., Dokumov, S.I, *Effect of ovarian wedge resection for the Stein-Leventhal syndrome on plasma FSH, LH, oestradiol and testosterone levels and on the responses of the pituitary to intravenous LHRH. . British journal of obstetrics and gynaecology* (1977)

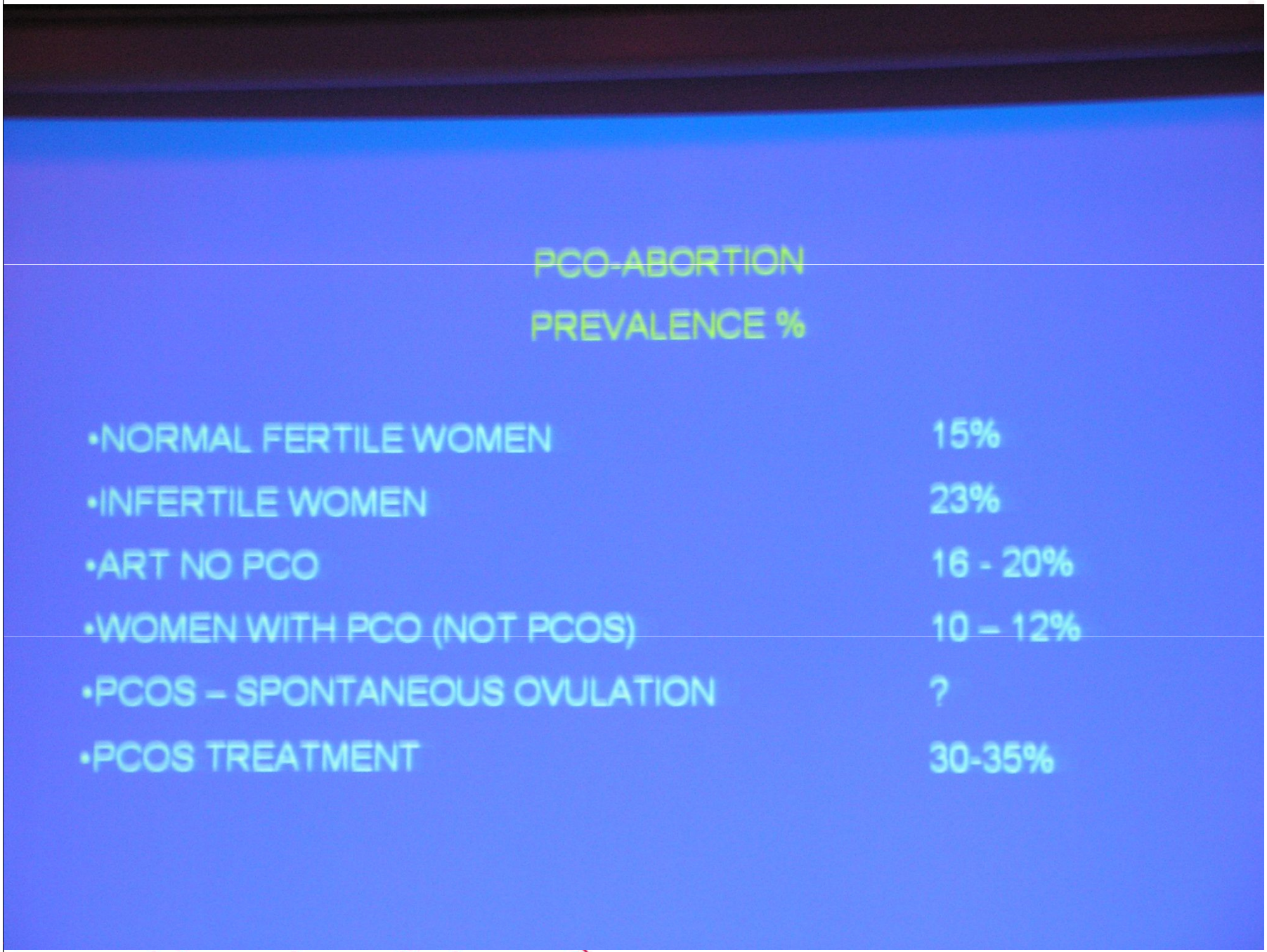
- Shterev A. D., Dokumov S I, *Serum LH and FSH levels in women with polycystic ovary syndrome before and after ovarian wedge resection*, Endocrinologie (1982)

-Shterev A. D. , S I Dokumov , *Serum LH-RH levels before and after ovarian wedge resection in polycystic ovary syndrome*, Endokrynologia Polska (1983)

-**Mohamed A.M Hassan, Stephen R Killick**
***Ultrasound diagnosis of polycystic ovaries in women who have no symptoms of polycystic ovary syndrome is not associated with subfecundity or subfertility*, Fertility and Sterility Vol. 80, (2003)**

The combination of the two approaches leads to the following conclusions





Therapy

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Patients with acne, alopecia and most of all with hirsutism combined with menstrual disorder or anovulation have been treated by **wedge resection of the ovary** for many years previously and many modification have been applied – microtechnique, non-resorbing threads etc. Nowdays this surgical procedure is replaced by **drilling of the ovaries** in PCO patients – a manipulation which together with the benefits bring a lot of damages for the patients, particularly with its current wide application in each lapascopy intervention.

Therapy

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Coming back to the treatment of **acne, hirsutism and alopecia** it should pointed out that the clinical experience shows that nevertheless the **specific therapies** the basic approach to treat the disease is decreasing or blocking the activity of the HPO axis in parallel with antiandrogenic therapy.

Therapy

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ACNE	HYRSUTISM	ALOPECIA
Cleansing lotions, cremes, antibiotics Accutane (isotretinoin)	Cosmetics, epilation, bleaching	Procedures increasing the blood supply of the affected zones Accutane (isotretinoin)
Inhibition of the HPO axis, antiandrogenic drugs with traditional therapy for the specific dermatologic disorders	Inhibition of the HPO axis, antiandrogenic drugs with traditional therapy for the specific dermatologic disorders	Inhibition of the HPO axis, antiandrogenic drugs with traditional therapy for the specific dermatologic disorders

Therapy

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5-alpha reductase inhibitors are ineffective in women because they hit the wrong target by trying to inhibit the metabolism of a hormone that is practically absent; whereas, a topical therapy with **estrone or 17 alpha estradiol may be effective** in many cases.

Only few drugs currently have US Food and Drug Administration (FDA)–approved indications for treatment of androgenetic alopecia:

- Minoxidil - mechanism of action is not known;
- Dutasteride - inhibits type I and type II 5-a reductase isoenzymes;
- Estron or Estradiol;

- Low-level laser light therapy.

Therapy

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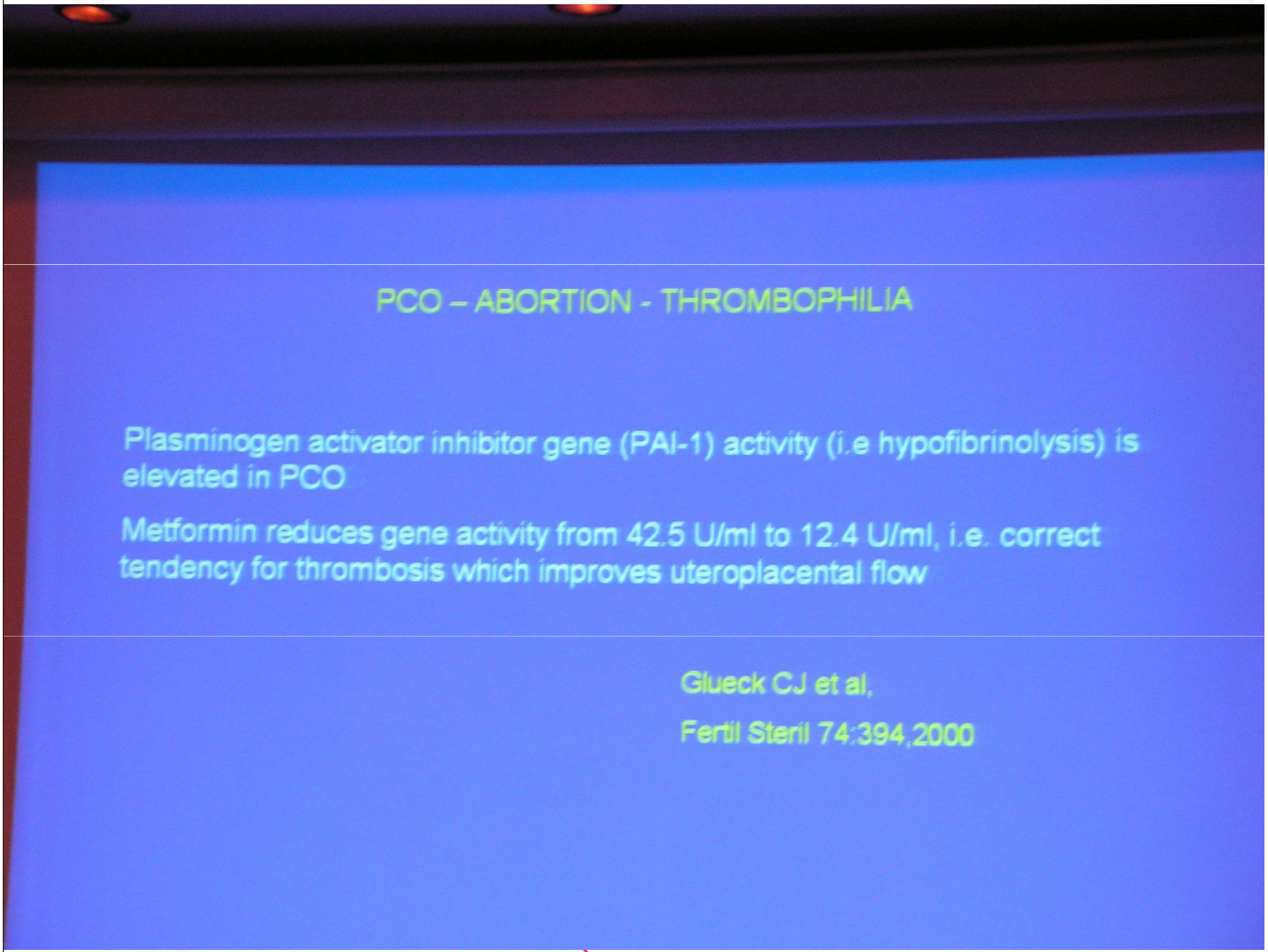
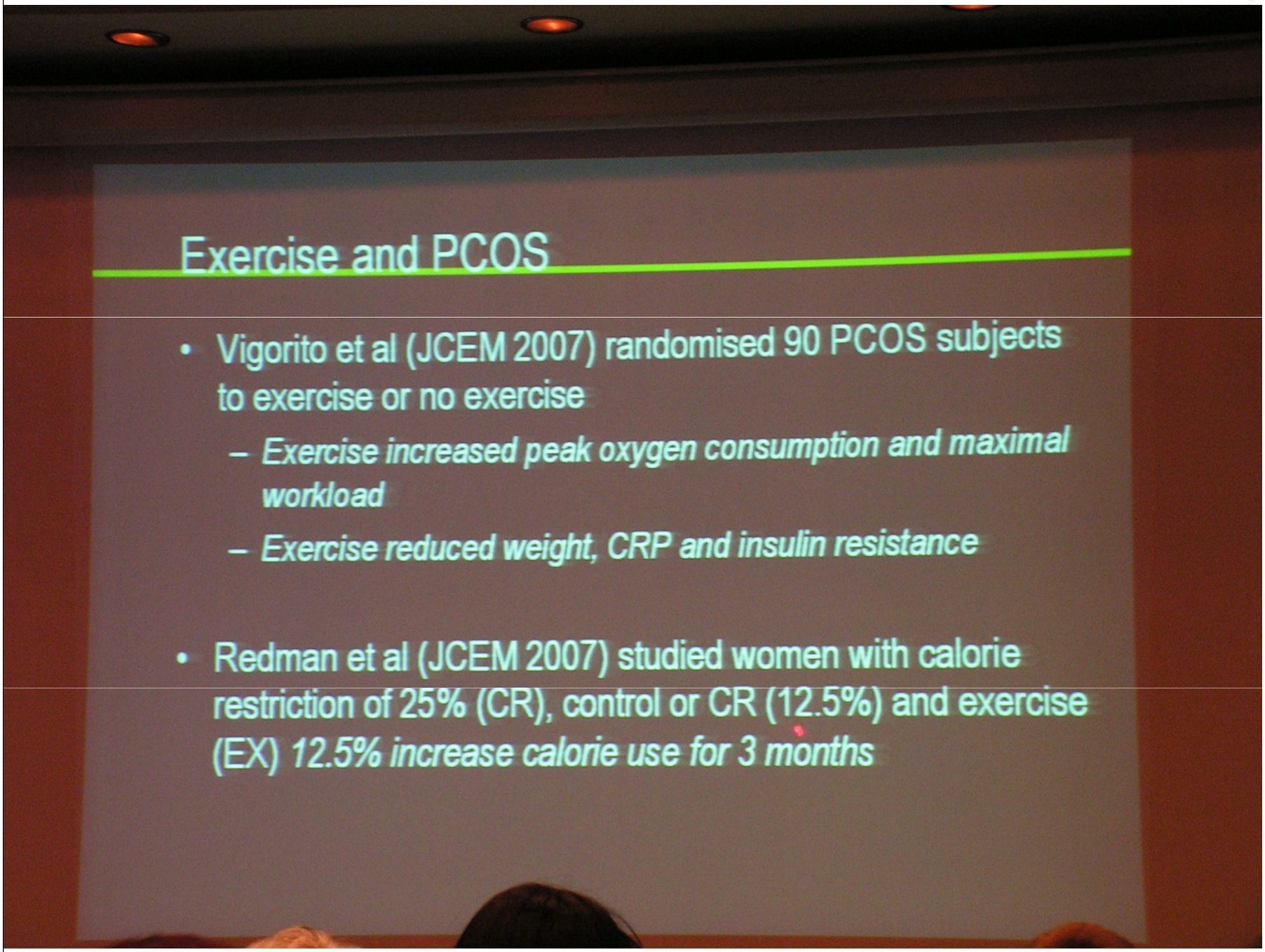
Efstathiadou et al. (2001) report an example of long-term remission of ovarian hyperandrogenism in a postmenopausal woman, after **short-term treatment with GnRH-a triptorelin.** Testosterone levels remained normal and the patient was asymptomatic for an observation period of 3 years.
This supports the view that GnRH-a therapy could be used, even in short courses, for the long-term suppression of benign ovarian hyperandrogenism.
This claim is contrary to the statement of Leyendecker and G., Wildt, L. (1983).

Z.Efstathiadou, A.Tsatsoulis. *Long-term remission of ovarian hyperandrogenism after short-term treatment with a gonadotropin-releasing hormone agonist,*Fertility and Sterility, Volume 75, Issue 1, January 2001, Pages 59-62

Leyendecker and G., Wildt, L (1983) *Induction of Ovulation with Chronic Intermittent (Pulsatile) Administration of Gn-RH in Women with Hypothalamic Amenorrhoea,* Journals of Reproduction & Fertility , 69, p. 397-409


PCO – ABORTION - THROMBOPHILIA
Plasminogen activator inhibitor gene (PAI-1) activity (i.e hypofibrinolysis) is elevated in PCO
Metformin reduces gene activity from 42.5 U/ml to 12.4 U/ml, i.e. correct tendency for thrombosis which improves uteroplacental flow
Glueck CJ et al,
Fertil Steril 74:394,2000


Exercise and PCOS
• Vigorito et al (JCEM 2007) randomised 90 PCOS subjects to exercise or no exercise
– Exercise increased peak oxygen consumption and maximal workload
– Exercise reduced weight, CRP and insulin resistance
• Redman et al (JCEM 2007) studied women with calorie restriction of 25% (CR), control or CR (12.5%) and exercise (EX) 12.5% increase calorie use for 3 months

Gene therapy

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The first step is figuring out which of the tens of thousands of genes on strands of DNA are involved in the characteristic to be altered. In a given individual with androgenetic alopecia (pattern hair loss), some hair follicle cells will express the characteristic of DHT-resistance (the follicles at the back of the scalp), while other hair follicles on the same person will express the characteristic of DHT-sensitivity (at the hairline, for example). Both follicles contain cells with identical DNA, but they express different characteristics.

The second step is figuring out how exactly the target genes are to be changed. The gene, called *hairless*, was mapped in **humans to chromosome 8p21**, and was the first example of a single gene defect being identified as a hair loss cause (Christiano et al. 1998).

The third step of gene therapy is delivering the new-and-improved genes to the target cells, and then to have those cells use the new genes to make the corresponding new proteins, and then to have the altered cells express the desired characteristic.

Conclusions:

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1/ There are several forms of hyperandrogenism which could be diagnosed and require different approaches towards treatment;

2/ PCO is not a disease itself but a symptom of a broad spectrum of diseases which are well defined;

3/ The most common occurrence of the different forms of acne, hirsutism, alopecia and anovulation can be observed in patients with HONTO (Hyperandrogenemia ovarialis from non tumor origin).

4/ When acne, hirsutism and alopecia are observed under HONTO, the basic treatment is blocking the activity of the HPO axis and administering antiandrogenic therapy along with specific therapy for each individual manifestation of the above mentioned conditions.

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Thank you for your attention!

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