International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2019): 7.583

# 5 Alpha - Reductase and Metabolic Syndrome in PCOS Patients

**Emirvina Koliçi**

University of Medicine, Medical Faculty of Technical Sciences, Tirana, Albania
e.kolici[at]yahoo.com

**Abstract:** ***Objectives: Polycystic ovary syndrome is one of the most common endocrine pathologies in fertile women. PCOS is an endocrine disorder characterized by a disorder of the reproductive and metabolic systems that include hyperandrogenism, ovarian dysfunction and morphological changes in the ovaries (presence of cysts) as well as other clinical and biochemical symptoms such as hirsutism, hyperinsulinemie, etc. alpha reductase deficiency is considered one of the causes of PCOS and total testosterone/dihydrotestosterone ratio (TT/DHT) it is used in the evaluation of its activity. Methods: In 70 cases diagnosed as PCOS, based on Rotterdam criteria we measured the serum levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone (TT) and DHT. TT/DHT ratio was calculated in order to reflect 5alpha-reductase activity. In all participants, anthropometric data, lipids, HOMA-IR were also assessed. Results: In cases of PCOS patients we measured the level of TT (0.87±0.79) (ng/ml),DHT (29.9±11.8)(ng/dl), FSH (5.7±2.06)(UI/L), LH (12.7±10.2)(UI/L). We calculate LH/FSH ratio (2.3±1.2) and TT/DHT ratio (3.1±1.7). PCOS patients showed significantly higher levels of TT than control group. The TT/DHT ratio was significantly higher in PCOS patients (P <.005). No difference was found for total DHT levels. The studied groups were not different in terms of age, BMI and HOMA-IR. In the patients group, mean TT levels were significantly higher as compared to controls. In the patients group, mean TT/DHT ratio was significantly higher compared to controls. The association between TT/DHT ratio and unfavorable metabolic parameters was also seen in controls. Conclusion: Total testosterone/dihydrotestosterone ratio correlates with a worse metabolic profile not only in PCOS patients, but also in healthy women.***

**Keywords:** testosterone, dihydrotestosterone, polycystic ovary syndrome, hyperandrogenism

## 1. Introduction

Polycystic ovary syndrome is one of the most common endocrine pathologies in fertile women. Stein and Leventhal originally described it in 1935.PCOS is an endocrine disorder characterized by a disorder of the reproductive and metabolic systems that include hyperandrogenism, ovarian dysfunction and morphological changes in the ovaries (presence of cysts) as well as other clinical and biochemical symptoms such as hirsutism, hyperinsuliema etc.. It is estimated that this pathology affects 4-12% of women.This pathology is characterized by a lack of follicular maturation and stromal hyperplasia associated with androgen hypersecretion. This production is assessed by dosing LH which results in high level.

The physiology of PCOS is concerned with;

1) Hyperandrogenism is the main feature of PCOS, it can even be called its defining feature. Hyperandrogenism is exacerbated by hyperinsulinemia. Similar ovarian characteristics have been observed in women with hyperandrogenism such as congenital and adrenal hyperplasia.
   - Neuroendocrine disorders: Women with PCOS have an increased frequency of GnRH secretion; which leads to increased production of luteinizing hormone (LH) and decreased production of follicle-stimulating hormone (FSH). Patients exhibit an increase in the LH / FSH ratio, which leads to an increase in ovarian androgens compared to estrogens. / an ovulation itself increases GnRH secretion through a decrease in circulating progesterone. Normally, progesterone is produced by the corpus luteum after ovulation and acts to slow down the pulse of GnRH. In PCOS, an ovulation disorder can cause a decrease in circulating progesterone, and exposure to androgens in the ovaries can reduce the inhibitory effects of estrogen and progesterone on the hypothalamus and contribute to increased GnRH production.
2) Insulin resistance. 50-70% of patients with PCOS exhibit metabolic abnormalities, including glucose tolerance and hyperinsulinemia. Insulin resistance is considered to be due to defects in glucose transport and signaling in adipocytes and myocytes; this may be the result of a disorder in adipokine production but the mechanism is not very clear. Hyperinsulinemia acts through IGF-1 receptors.
3) Polycystic ovaries. Polycystic ovaries are present in 20-30% of women with PCOS. Cysts are many antral follicles that are not fully developed. This is thought to occur due to hormonal abnormalities:

   - Hyperandrogenism: the increase in androgens leads to a decrease in the production of estradiol important for follicle maturation.
   - Hyperinsulinemia: exacerbates ovarian hyperandrogenism by (1) increasing 17a-hydroxylase activity by increasing androstenedione and testosterone production; (2) increased androgen production by stimulation of LH- and IGF1; and (3) increase free testosterone by reducing sex hormone binding globulin (SHBG) production. (35)

The PCOS clinic includes: Menstrual disorders: PCOS is mainly associated with oligomenorrhea (less than nine menstrual cycles per year) or amenorrhea (without menstrual cycles for three or more months in a row). (31) Infertility: This generally results directly from chronic an ovulation (31) High levels of male hormones: Known as

hyperandrogenism, the most common signs are acne and hirsutism but can also be associated with androgenic alopecia areata (31)

In a woman with PCOS we have high levels of FSH and LH which stimulate the production of androgens by the ovaries. This is accompanied by increased production of total testosterone which through 5 alpha reductase is converted to dehydrotestosterone (DHT) responsible for morphological and functional changes of the ovaries and as metabolic disorders of the body. Activity of 5 alpha reductase plays a key role in the formation of DHT which has a higher affinity for androgen receptors in the periphery and is responsible for clinical androgenic secondary sexual signs such as hirsutism, morphological and functional changes of the ovaries as well as metabolic disorders. Therefore, serial levels of total Testosterone (TT), DHT, as well as the evaluation of 5 alpha reductase activity through the TT / DHT ratio are considered as diagnostic indicators for the androgenic activity responsible for biochemical, clinical disorders in PCOS.

Metabolic Syndrome: This manifests as a tendency towards obesity and other symptoms related to insulin resistance. (31)

Metabolic syndrome is not a disease, but a group of risk factors (obesity, dyslipidemia, hyperglycemia and hypertension), which increase the risk of cardiovascular disease and type 2 diabetes mellitus. This can affect 25/30% of the total world population. In Europe it has reached 15% in the adult population.(11)

With metabolic syndrome are considered subjects who have had at least three of these factors:

1) Abdominal obesity (waist circumference ≥ 102 cm in men and ≥ 88 cm in women)
2) Triglycerides (≥1.7 mmol / l) or specific treatment for this disorder (fibrates or nicotinic acid)
3) HDL-cholesterol <1.03 mmol / l in men, <1.29 mmol / l in women or specific treatment for this disorder
4) Systolic blood pressure ≥ 130 mmHg and / or diastolic blood pressure ≥ 85 mmHg or treatment for hypertension
5) Hyperglycemia esell > 5.6 mmol / l or preliminary diagnosis for type II diabetes.

## 2. Material and methods

The study included about 70 patients diagnosed with PCOS in the age group of 16-40 years. This assessment was made by meeting the Rotterdam criteria which includes:

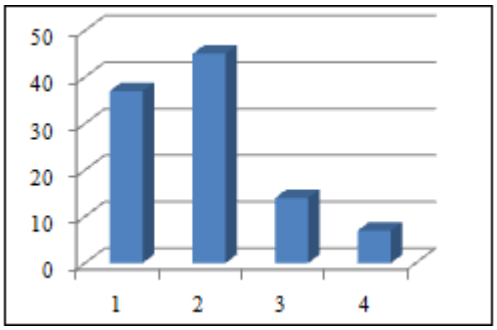
1) Oligo- or anovulation,
2) Clinical and / or biochemical signs of hyperandrogenism
3) Polycystic ovary (more than 12 cysts)

We also included examinations of biochemical examinations (glycemia, cholesterol, triglycerid and hormonal examinations involving FSH, LH, estradiol, prolactin, insulin, Testosterone, dehydrotestosterone, as well as the TT / DHT ratio for evaluating the activity of 5α reductase

The study also included 30 cases of control of women of childbearing age, clinically and metabolically normal

## 3. Results

Based on the collected data, the distribution of polycystic ovary by age groups is presented in the graph below where the highest percentage is occupied by the age of 20-30 years:

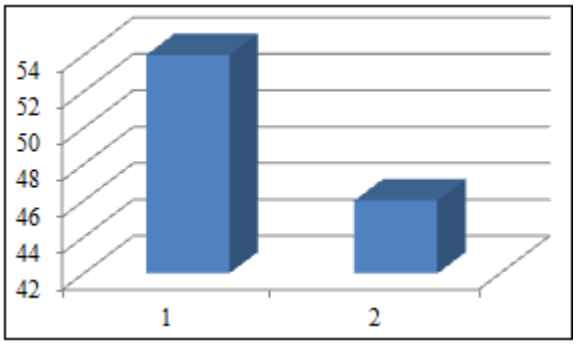



**Graph 1:** Distribution of PCOS by age: 16-20 years 37%, 21-30 years 45%, 31-35 years 14%, 35-40 years 7%.

Depending on the collected data, a distribution of clinical manifestations was observed in patients with pcos presented in Table 1

**Table 1:** Distribution of clinical manifestations was observed in patients with PCOS

| Manifestations of hyperandrogenism | | |
|---|---|---|
| Hirsutism | 52 | 78 |
| Manifestations of ovarian dysfunction | | |
| Oligomenorrhea | 56 | 80 |
| Amenorrhe | 11 | 15 |
| Cycle normal | 3 | 5 |
| Polycistic ovary in Echo | 62 | 89 |
| Obesity | 38 | 54 |



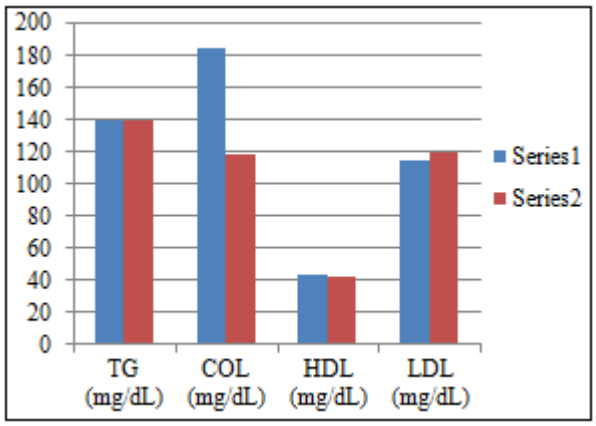

**Graph 2:** Presence of obesity in patients with PCOS

Biochemical manifestations in patients with polycystic ovaries are presented in Table 2

| Variabilat | Control | | |
|---|---|---|---|
| | PCOS | Group | P value |
| | | | |
| TG (mg/dL) | 140.6±70 | 140±35 | 0.6 |
| COL (mg/dL) | 185±33 | 119±45 | 0.6 |
| HDL (mg/dL) | 43.3±7.2 | 43±5.3 | 0.8 |
| LDL (mg/dL) | 115±24 | 120±27 | 0.5 |

Table number 2, Mean ± SD values of lipids between patients with PCOS and the control group as well as the

value of p using Student-test. In this case no significant relationship was observed between the control group and patients with polycystic ovary.

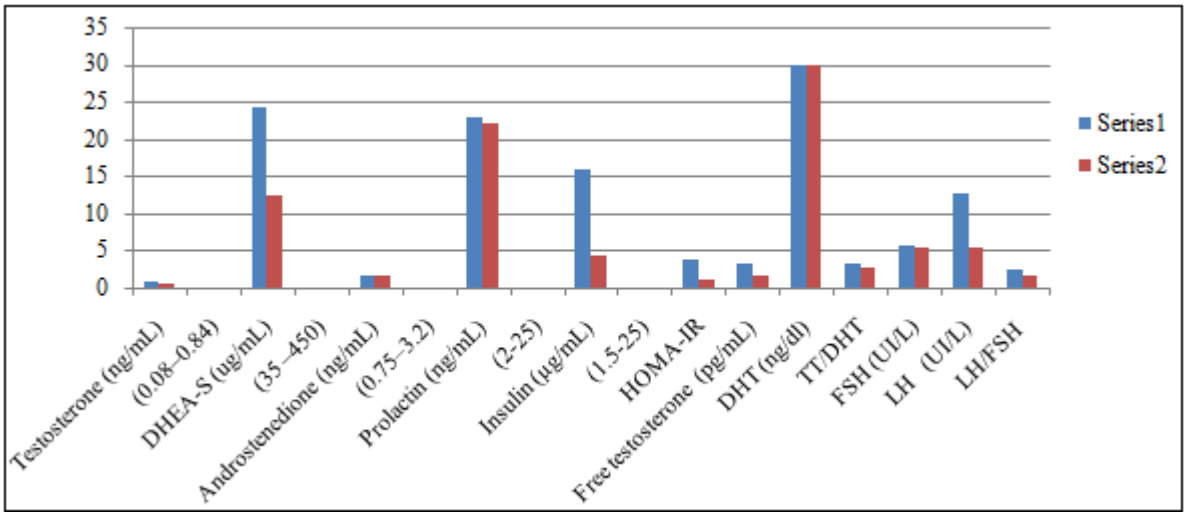



**Graph 3:** Relationship of metabolic factors between patients with PCOS and the control group

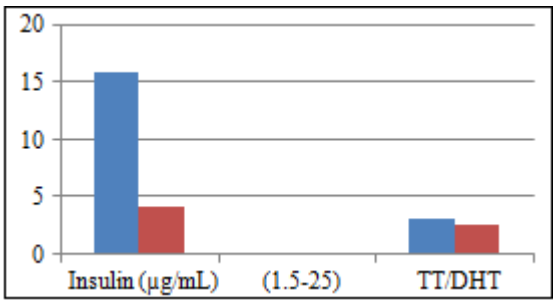
Hormonal manifestations in patients with polycystic ovaries are presented in Table No. 3

| Variabilat | Control | | |
|---|---|---|---|
| | PCO | Group | P value |
| Testosterone (ng/mL) (0.08–0.84) | 0.89±0.1 | 0.6±0.05 | 0.7 |
| DHEA-S (ug/mL) (35 –450) | 241 ±120 | 124 ±131 | 0.001* |
| Androstenedione (ng/mL) (0.75–3.2) | 1.7±0.4 | 1.5±0.4 | 0.3 |
| Prolactin (ng/mL) (2-25) | 22.8±12 | 22.1±2.2 | 0.7 |
| Insulin (µg/mL) (1.5-25) | 16±1.4 | 4.2±1.8 | 0.001 |
| HOMA-IR | 3.7±3.3 | 1.1±0.9 | 0.001 |
| Free testosterone (pg/mL) | 3.2±0.1 | 1.6±0.1 | 0.05 |
| DHT (ng/dl) | 29.9±11.8 | 30±10 | 0.7 |
| TT/DHT | 3.1±1.7 | 2.7±1.3 | 0.01 |
| FSH (UI/L) | 5.7±2.06 | 5.3±1.6 | 0.51 |
| LH (UI/L) | 12.7±10.2 | 5.37± | 0.4 |
| LH/FSH | 2.3±1.2 | 1.6±1.2 | 0.001 |

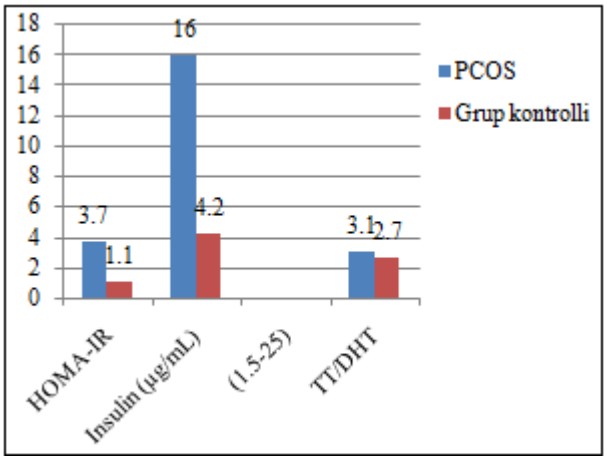
Table No. 3. Comparison between control group and PCOS
In this case a significant association was observed between the control group and Patients with PCOS in the case of insulin (p <0.001), HOMA-IR (P <0.001). In the case of androgens a significant correlation was observed in the case of the TT / DHT ratio (P <0.01) Free Testosterone (P <0.05) as well as the LH / FSH ratio (p <0.001)




**Graph 4:** Binding of hormonal components between patients with PCOS and the control group




**Graph 5:** Relationship between TT / DHT ratio and insulin between PCOS patients and control group




**Graph 6:** Relationship between TT / DHT ratio, HOMA-IR, insulin between PCOS patients and control group

**Table 8:** Evaluation of metabolic data by estimating the median and percentiles in the control group and patients with PCOS

| | Control group (n = 30) | | | PCOS (n = 75) | | | *P* Value |
|---|---|---|---|---|---|---|---|
| | Median | 25th Percentile | 75th Percentile | Median | 25th Percentile | 75th Percentile | |
| Mosha | 35.8 | 27.7 | 42 | 26 | 22 | 30 | <.001 |
| Pesha (kg) | 70.5 | 62 | 89 | 69 | 59 | 88.1 | .716 |
| BMI (kg/m$^2$) | 25.2 | 20.9 | 31.1 | 24.8 | 21.4 | 31.6 | .755 |
| Glicemia esell | 89.5 | 83 | 92.5 | 87 | 81 | 93 | .304 |
| Insulina esell (μIU/mL) | 4.7 | 2.3 | 7.3 | 7.2 | 4.2 | 12.7 | .001 |
| Cholesterol (mg/dL) | 181.5 | 157.5 | 218.5 | 179.5 | 156 | 200 | .301 |
| Triglycerid (mg/dL) | 62.5 | 47.5 | 81.7 | 76.5 | 54 | 109.2 | .055 |
| HDL (mg/dL) | 72 | 59 | 86 | 63 | 50 | 78 | .004 |
| LDL (mg/dL) | 89 | 76 | 129 | 98 | 83 | 117 | .590 |
| HOMA-IR | 1 | 0.4 | 1.6 | 1.5 | 0.9 | 2.8 | .003 |
| Testosterone (ng/mL) | 0.3 | 0.27 | 0.44 | 0.5 | 0.38 | 0.69 | <.001 |
| DHT (ng/mL) | 0.11 | 0.07 | 0.14 | 0.12 | 0.08 | 0.17 | .072 |
| TT/DHT ratio | 3.1 | 2.7 | 4.2 | 4.3 | 3.1 | 5.9 | < 0.01 |

## 4. Conclusions

In patients with PCOS an increase in the TT / DHT ratio was observed and the correlation of this ratio with other hormonal and metabolic parameters was observed.

In patients with PCOS alone an increase in TT / DHT was observed in obese patients (BMI> 30)

A decrease in DHT levels was also observed in obese patients. We estimate that an increase in TT / DHT may serve as a risk factor for metabolic syndrome in patients with PCOS.

Increased TT / DHT has a positive correlation with glucose metabolism because a statistically significant relationship was observed between glucose intolerance, insulin resistance, HOMA and other metabolic factors such as triglycerides, cholesterol.

From this we conclude that the TT / DHT ratio can serve as an indicator of the risk of developing metabolic syndrome and insulin resistance in patients with PCOS

## References

[1] Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5*α*-reductase-2 deficiency. *Molecular and Cellular Endocrinology*. 2002;198(1-2):51–59

[2] Siiteri PK, Wilson JD. Testosterone formation and metabolism during male sexual differentiation in the human embryo. *Journal of Clinical Endocrinology and Metabolism*. 1974;38(1):113–125.

[3] Cilotti A, Danza G, Serio M. Clinical application of 5*α*-reductase inhibitors. *Journal of Endocrinological Investigation*. 2001;24(3):199–203.

[4] Imperato McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5*α* reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science*. 1974;186(4170):1213–1215.

[5] Saartok T, Dahlberg E, Gustafsson JA. Relative binding affinity of anabolic-androgenic steroids: comparison of the binding to the androgen receptors in skeletal muscle and in prostate, as well as to sex hormone-binding globulin. *Endocrinology*. 1984;114(6):2100–2106.

[6] Beato M. Gene regulation by steroid hormones. *Cell*. 1989; 56(3):335–3447. Stiles AR, Russell DË. SRD5A3: a surprising role in glycosylation. *Cell*. 2010;142(2):196–198. [

[7] Langlois VS, Zhang D, Cooke GM, Trudeau VL. Evolution of steroid-5*α*-reductases and comparison of their function with 5*β*-reductase. *General and Comparative Endocrinology*. 2010; 166(3):489–497.

[8] Aggarwal S, Thareja S, Verma A, Bhardwaj TR, Kumar M. An overview on 5*α*-reductase inhibitors. *Steroids*. 2010;75(2):109–153

[9] Eicheler Ë, Dreher M, Hoffmann R, Happle R, Aumuller G. Immunohistochemical evidence for differential distribution of 5*α*-reductase isoenzymes in human skin. *British Journal of Dermatology*. 1995; 133(3):371–376.

[10] Aumüller G, Eicheler Ë, Renneberg H, Adermann K, Vilja P, Forssmann ËG. Immunocytochemical evidence for differential subcellular localization of 5*α*-reductase isoenzymes in human tissues. *Acta Anatomica*. 1997;156(4):241–252.

[11] Bayne EK, Flanagan J, Einstein M, et al. Immunohistochemical localization of types 1 and 2 5*α*-reductase in human scalp. *British Journal of Dermatology*. 1999;141(3):481–491

[12] Thigpen AE, Silver RI, Guileyardo JM, Casey ML, McConnell JD, Russell DW. Tissue distribution and ontogeny of steroid 5*α*-reductase isozyme expression. *Journal of Clinical Investigation*. 1993; 92(2):903–910.

[13] Thomas LN, Douglas RC, Lazier CB, Too CKL, Rittmaster RS, Tindall DJ. Type 1 and type 2 5*α*-reductase expression in the development and progression of prostate cancer. *European Urology*. 2008; 53(2):244–252.

[14] Söderström TG, Bjelfman C, Brekkan E, et al. Messenger ribonucleic acid levels of steroid 5*α*-reductase 2 in human prostate predict the enzyme activity. *Journal of Clinical Endocrinology and Metabolism*. 2001; 86(2):855–858.

[15] Habib FK, Ross M, Bayne CW, et al. The localisation and expression of 5*α*-reductase types I and II mRNAs in human hyperplastic prostate and in prostate primary

cultures. *Journal of Endocrinology*. 1998; 156(3):509–517.
[16] Bonkhoff H, Stein U, Aumüller G, Remberger K. Differential expression of 5*α*-reductase isoenzymes in the human prostate and prostatic carcinomas. *The Prostate*. 1996;29(4):261–267.
[17] Shirakawa T, Okada H, Acharya B, et al. Messenger RNA levels and enzyme activities of 5 alpha-reductase types 1 and 2 in human benign prostatic hyperplasia (BPH) tissue. *The Prostate*. 2004;58(1):33–40.
[18] Titus MA, Gregory CW, Ford OH, Schell MJ, Maygarden SJ, Mohler JL. Steroid 5*α*-reductase isozymes I and II in recurrent prostate cancer. *Clinical Cancer Research*. 2005;11(12):4365–4371.
[19] Godoy A, Kaëinski E, Li Y, et al. 5*α*-reductase type 3 expression in human benign and malignant tissues: a comparative analysis during prostate cancer progression. *The Prostate*. 2011;71(10):1033–1046.
[20] Yamana K, Labrie F, Luu-The V, et al. Human type 3 5*α*-reductase is expressed in peripheral tissues at higher levels than types 1 and 2 and its activity is potently inhibited finasteride and dutasteride. *Hormone Molecular Biology and Clinical Investigation*. 2010;2(3):293–299. [
[21] Moss GP. Nomenclature of steroids (Recommendations 1989) *Pure and Applied Chemistry*. 1989;61(10):1783–1822.
[22] P. A. Lee, C. P. Houk, S. F. Ahmed et al., "Consensus statement on management of intersex disorders," Pediatrics, vol. 118, no. 2, pp. e488–e500, 2006.
[23] J. Imperato-McGinley and Y. S. Zhu, "Androgens and male physiology the syndrome of 5α-reductase-2 deficiency," Molecular and Cellular Endocrinology, vol. 198, no. 1-2, pp. 51–59, 2002.
[24] Y. Morel, R. Rey, C. Teinturier et al., "Aetiological diagnosis of male sex ambiguity: a cllaborative study," European Journal of Pediatrics, vol. 161, no. 1, pp. 49–59, 2002.
[25] G. H. G. Sinnecker, O. Hiort, L. Dibbelt et al., "Phenotypic classification of male
[26] pseudohermaphroditism due to steroid 5α-reductase 2 deficiency," American Journal of Medical Genetics, vol. 63, no. 1, pp. 223–230, 1996. ·
[27] S. F. Ahmed, O. Khëaja, and I. A. Hughes, "The role of a clinical score in the assessment of ambiguous genitalia," BJU International, vol. 85, no. 1, pp. 120–124, 2000.
[28] P. N. Gabrich, J. S. P. Vasconcelos, R. Damião, and E. A. Da Silva, "Penile anthropometry in Brazilian children and adolescents," Jornal de Pediatria, vol. 83, no. 5, pp. 441–446, 2007.
[29] P. A. Tomasi, "Sex determination, differentiation, and identity," The Neë England Journal of Medicine, vol. 350, no. 21, pp. 2204–2204, 2004.
[30] Lorena I. Rasquin Leon; Jane V. Mayrin. Polycystic Ovarian Disease (Stein-Leventhal Syndrome)
[31] Teede H, Deeks A, Moran L (2010). *"Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan"*. *BMC Med*. **8** (1): 41. *doi:10.1186/1741-7015-41*. *PMC 2909929*. *PMID 20591140*
[32] *J Obstet Gynaecol Can*. 2010 May;32(5):423-5, 426-8.
[33] *Nat Rev Endocrinol*. 2011 Apr;7(4):219-31.
[34] *N Engl J Med*. 2005 Mar 24;352(12):1223-36.
[35] *Alexandra Rotstein*. "Polycystic ovary syndrome
[36] Ferriman D, GallweyJD 1961 Clinical assessment of body hair groëth in women.*J Clin*