APPENDICES

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APPENDIX 1

LIST OF INTERNATIONAL MEDICAL EXPERTS

	Name	Area of Expertise
1	Prof. Martin Ritzen (SWE) (Chairman)	Pediatrics/endocrinology
2	Prof. Peter Lee (USA)	Pediatrics/endocrinology
3	Prof. Berenice Mendonca (BRA)	Endocrinology/genetics
4	Prof. Tsutomu Ogata (JAP)	Genetics
5	Prof. Zi-Jiang Chen (CHN)	Gynecology/Polycystic ovary syndrome
6	Prof. Garry Warne (AUS)	Pediatrics/endocrinology
7	Prof. Patrick Fenichel (FRA)	Gynecology/endocrinology
8	Prof. Angelica Lindén Hirshberg (SWE)	Gynecology/endocrinology
9	Prof. Myron Genel (USA)	Pediatrics/endocrinology
10	Prof. Ieuan Hughes (UK)	Pediatrics/endocrinology
11	Prof. Joe Leigh Simpson (USA)	Genetics/obstetrics/gynecology
12	Prof. Peggy Cohen-Kettenis (NED)	Psychology
13	Dr. Rinus Wiersma (RSA)	Pediatrics/surgery
14	Prof. Maria New (USA)	Pediatrics/genetics

APPENDIX 2

MEDICAL GUIDELINES FOR THE CONDUCT OF
LEVEL 1 AND LEVEL 2 EXAMINATIONS

This practical document has been written to assist medical doctors in the screening, evaluation and specialist referral of virilised female athletes.

It is divided into the following parts:

A - Hyperandrogenism and virilisation syndrome in female athletes: Introduction

B - Important elements of history taking and clinical signs

C - Useful scoring systems

D –Endocrine Assessment: essentials

References:

- American Association of Clinical Endocrinologists (AACE) - **Medical guidelines for the clinical practice for the diagnosis and treatment of hyperandrogenic disorders** - ENDOCRINE PRACTICE Vol. 7 No. 2 March/April 2001 Hyperandrogenic Disorders Task Force Chairman Neil F. Goodman, MD, FACE https://www.aace.com/files/hyper-androgenism-2001.pdf

- Lee PA, Houk CP, Ahmed SF, Hughes IA; International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. **Consensus statement on management of intersex disorders**. International Consensus Conference on Intersex. Pediatrics. 2006 Aug;118(2):e488-500. PubMed PMID: 16882788. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2082839/

A - Hyperandrogenism and virilisation syndrome in female athletes: Introduction

Hyperandrogenism in female athletes is a clinical condition that should always be thoroughly investigated to ensure a clear diagnosis.

Except for idiopathic hirsutism, virilisation results from the presence of abnormally high levels of androgens, the principal androgenic hormone being testosterone. The cause of the raised level may be either endogenous (e.g., a tumor or functional endocrine disorder) or it may be exogenous (oral or parenteral administration of synthetic androgens). There is a medical consensus supporting early diagnosis and careful follow-up of all cases.

Hyperandrogenism is associated with certain specific clinical features, including hyperseborrhea, acne and hirsutism. In more severe cases, there may be hoarseness and deepening of the voice, alopecia, muscular hypertrophy and clitoromegaly.

Moderate hyperandrogenism is not uncommon in women, and is usually linked to hormonal dysfunction. Its consequences will have different expressions according to the age of the patient and the date of onset. Polycystic Ovarian Syndrome (PCOS) is the most common diagnosis, often associated with menstrual disturbances and infertility. Early diagnosis can often help to improve these conditions, avoid metabolic disorders, and possibly reduce the risk of later cardiovascular events and gynaecological cancers.

The development of hyperandrogenism depends on both an excessively high level of circulating androgen and normal androgen sensitivity of the receptor tissues.

A serious underlying medical condition should always be suspected if the onset of symptoms is fast and/or intense. Although rare, the possibility of an androgen-secreting tumor should always be investigated.

The exogenous administration of doping agents (anabolic steroids), as well as Disorders in Sex Development (DSD), should also be excluded.

Investigation requires careful history-taking and clinical examination to ensure accurate diagnosis and appropriate treatment.

B - Important elements of history taking, and clinical signs

Listed below are the main anamnestic and clinical elements used for screening, evaluation and referral of the patient for more specialist care. Evaluation must include an assessment of the severity of the condition. The first medical examination is usually performed by a Sports Physician, either alone or together with a specialist. This is followed by a specialist examination performed by an experienced Gynecologist or Gynecological Endocrinologist, or a Pediatrician if the patient is under 15 years old.

=> Sports Medicine Examination
This represents a basic but very important step. This examination should be included as part of the « Pre Participation Medical Examination » (PPME) as anticipated by the IAAF) or the complementary « Periodic Health Examination » (PHE) as designed by the IOC). More practical information and guidelines about the IOC Consensus Statement on Periodic Health Evaluation of Elite Athletes can be downloaded here.

=> Specialized Examination
This examination must be performed by a gynaecologist, endocrinologist or pediatrician who has extensive experience of all conditions relating to hyperandrogenism and DSD.

I - Medical History: Sports Physician &/or Gynecologist

Family history

1. Are the parents related to each other?
2. If so, describe relationship (attach a family tree)
3. Number of siblings (male/female)
4. Does anyone in the extended family have similar symptoms of hyperandrogenism? (If yes, describe in detail and indicate in the family tree)
5. Are there any family members with fertility problems/childless marriages?
6. Was the mother virilised during pregnancy?
7. Ethnic background (Caucasian, African, Asian, etc.)

Birth history

8. Birth weight (kg)
9. Birth length (cm)
10. Ambiguous genitalia at birth?
    a. If so, describe.
    b. Hospital records from neonatal period?
    c. Name of hospital

Pubertal history

11. Age at start of :
    a. pubic hair:
    b. breast buds:
    c. acne:
    d. deepening of voice:
    e. menstruation (menarche)
12. Menstruation characteristics
    a. ever menstruated?: Yes No
    b. regular: Yes / No (Indicate periodicity and duration of menses.)
    c. irregular: Yes / No (Describe in detail.)
    d. date of last menstruation:

Medical History

13. Previous illnesses and operations
14. Any pregnancies?
15. Ever hospitalized?
    a. If so, name and address of hospital
    b. Reason for admission

Medication

16. Ever had long term medication?
    a. If so, brand name?
    b. Why was this prescribed?
17. Ever had hormonal medication?
    a. If so, brand name?
    b. Why was this prescribed?
18. Ever used oral contraceptives?
    a. If so, brand name?
    b. Ongoing oral contraception?
19. Any ongoing medication?
    a. If so, brand name?
    b. Why was this prescribed?
20. Do you ever remove body or facial hair?
    a. If so, how often? How much? By what method(s)?
21. Any non-prescription medication?

II - Physical examination Sports Physician & Gynecologist

General physical examination, including

1. Height:
2. Weight:
3. BMI:
4. Sitting height:
5. Body build:
6. Bi-acromial & bi-lliac breadths:
7. Adam's apple?
8. Deep voice?

Skin

9. Body hair:
10. Receding frontal hairline?
11. Loss of scalp hair?
12. Facial hair (Shaving? How often?)
13. Oily skin on face?
14. Apocrine sweat odour?
15. Abnormal pigmentation?
16. Cutaneous striae?

Circulation

17. Blood pressure:
18. Pulse rate:

Abdomen

19. Palpable masses?

Pubertal signs (Preferably assessed by a gynecologist or endocrinologist)

20. Breast (indicate Tanner-Whitehouse stage I-V (cf. schema below)
21. Horizontal diameter by palpation, lying down:
22. Areolar diameter:
23. Pubic hair (indicate Tanner-Whitehouse stage I-V) (cf. schema below)
24. Midline pubic hair extending towards umbilicus?

Genitalia (To be performed by Gynecologist-endocrinologist or Pediatrician-endocrinologist for girls of <15 yrs)

25. Detailed measurements and vaginal palpation to be reserved for the gynaecologist or paediatrician. (Vaginal examination may possibly require general anaesthesia, especially if the patient is young.)
26. Clitoral enlargement? Length and width?
27. Abnormal size of labiae minora or majora?
28. Posterior fusion of labiae? Ano-genital distance:
29. Are any lumps palpable in labiae or in inguinal canals?
30. Is uterus or prostate palpable per rectum?

<u>Keys points</u> Which clinical signs suggest pronounced and chronicle hyperandrogenism?

- Deep voice
- Breast atrophy
- Never menstruation (or loss of menses since several month)
- Increased muscle mass
- Body hair of male type (vertex alopecia, >17 years)
- Tanner score low (I / II)
- F&G score (>6 / ! minimized by the beauty)
- No uterus
- Clitoromegaly

C - Scores and schemes

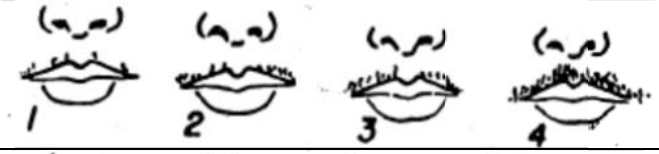
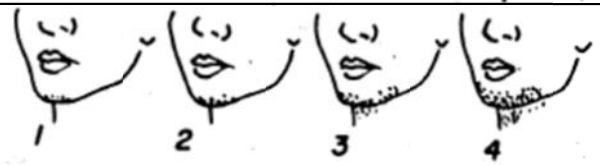
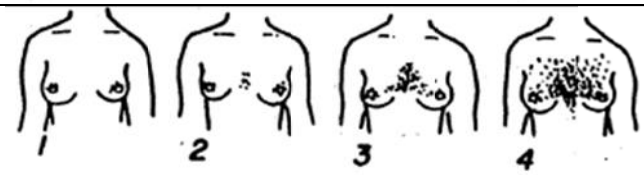
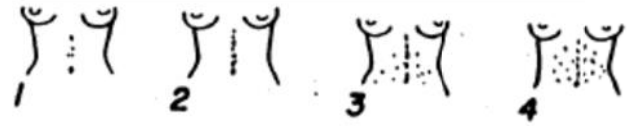
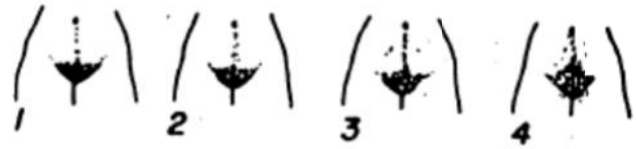
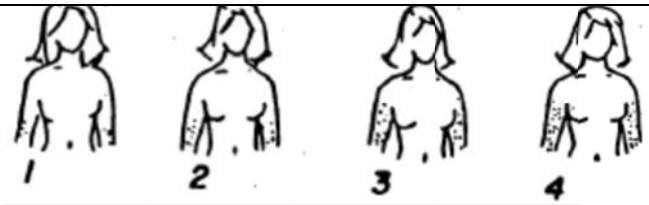
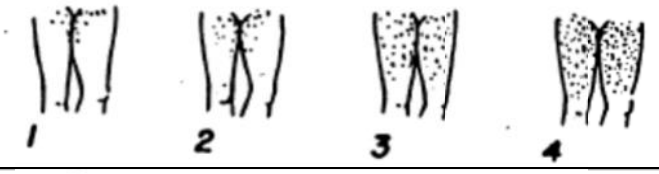
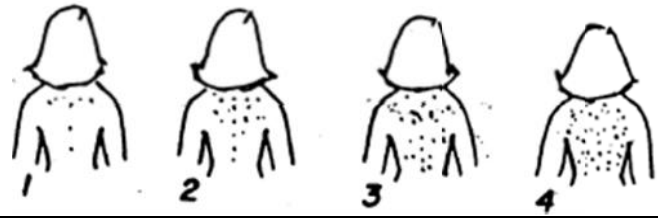
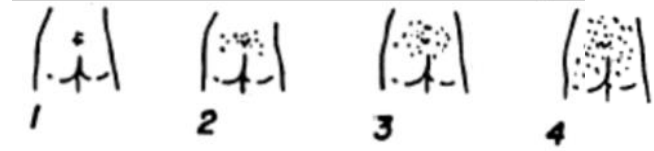
Hirsutism scoring sheet according to Ferriman and Gallwey

(Grade 0 at all sites indicates absence of terminal hair)

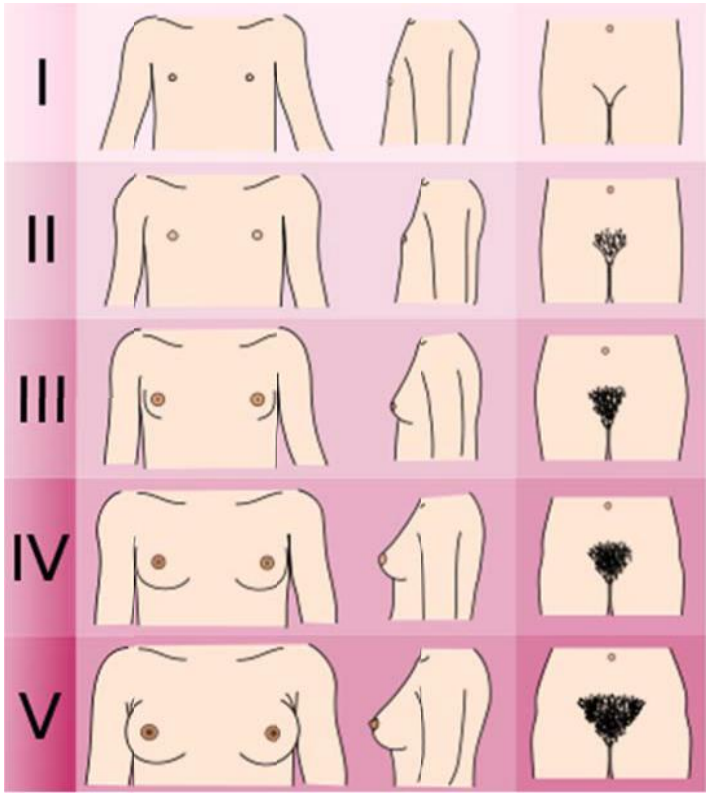
Upper Lip	1	A few hairs at outer margin
	2	A small moustache at outer margin
	3	A moustache extending halfway from outer margin
	4	A moustache extending to mid-line
Chin	1	A few scattered hairs
	2	Scattered hairs with small concentration
	3 et 4	Complete cover, light and heavy
Chest	1	Circumareolar hairs
	2	With mid-line hairs in addition
	3	Fusion of these areas, with three quarter cover
	4	Complete cover
Upper back	1	A few scattered hairs
	2	Rather more, still scattered
	3 et 4	Complete cover, light and heavy
Lower back	1	A sacral tuft of hairs
	2	With some lateral extension
	3	Three-quarter cover
	4	Complete cover
Upper abdomen	1	A few mid-line hairs
	2	Rather more, still mid-line
	3 et 4	Half and full cover
Lower abdomen	1	A few mid-line hairs
	2	A mid-line streak of hair
	3	A mid-line band of hair
	4	An inverted V-shaped growth
Arm / Thigh / Leg	1	Sparse growth affecting no more than a quarter of limb surface
	2	More than this; cover still incomplete
	3 et 4	Complete cover, light and heavy.
Forearm	1	Complete cover of dorsal surface
	2	Light growth
	3 et 4	Heavy growth

Score interpretation according to Abraham	Score value	
Normal	< 8	Biological investigations should be performed for scores over 16
Light hirsutism	8 to 16	
Moderate hirsutism	17 to 25	
Frank hirsutism	> 25	

Hirsutism scoring sheet according to Ferriman and Gallwey
(Grade 0 at all sites indicates absence of terminal hair)

Body Area	Date of exam :		
Upper Lip		Score	
Chin		Score	
Chest		Score	
Upper Abdomen		Score	
Lower Abdomen		Score	
Arms		Score	
Thigh		Score	
Upper Back		Score	
Lower Back		Score	
	TOTAL SCORE		

Tanner-Whitehouse Scale (female)



Tanner I

- No glandular tissue; areola follows the skin contours of the chest (pr epubertal) [typically age 10 and younger]

Tanner II

- Breast bud forms, with small area widen [10-11.5] of surrounding glandular tissue ; areola begins to widen [10-11.5]

Tanner III

- Breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast [11.5-13]

Tanner IV

- Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast [13-15]

Tanner V

- Breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla. [15+]

D – Endocrine assessment: essentials

Once a medical history has been established and a thorough clinical examination conducted, an endocrine assessment is usually necessary to make an etiological diagnosis. The laboratory tests will often make it possible to distinguish between different causes of severe hyperandrogenism, in particular tumors, and ovarian or adrenal functional disorders. It is advisable to proceed step by step, doing a more limited blood test initially for screening purposes, and then further tests only if indicated.

The first parameter to be measured is the total testosterone as this level correlates well to the severity of clinical signs and symptoms.

This blood test must be performed:

- between the third and the eighth day of the menstrual cycle (or after the release of menses by a short course of didrogesterone 10 mg daily for 7 days in amenorrheic or oligomenorrheic patients)
- between 8 am and 10 am in the morning
- these precautions are necessary to avoid errors due to circadian and cyclic fluctuations in the blood levels of these hormones.

Interaction with certain other medications has to be taken into account, especially if the patient is taking estrogens and/or progestagens or glucocorticosteroids. A wash out period from these treatments should therefore be considered prior to investigation.

<u>Key points</u>
What hormones/substances should be measured at first-line screening?

In Blood:
- T plasmatic (reflection of ovarian, adrenal or mixed production)
- SHBG (allows the calculation of the Free Androgen Index)
- 17-OHP (plasma marker of the block in 21-hydroxylase)
- DHEAS (reflection of the adrenal metabolism)

In Urine:
- Testosterone
- Epitestosterone
- Androsterone
- Etiocholanolone
- Dihydrotestosterone
- 5α-androstan-3a, 17b-diol
- 5β-androstan-3a, 17b-diol
- Dehydroepiandrosterone

Additional blood parameters may be measured at the same time as the first-line screening - according to the expert's diagnostic orientation - or as part of a second round of analyses - according to the expert's diagnostic orientation or at the request of the IAAF Medical Director:
- Delta 4 Androstenedione,
- LH
- FSH
- Prolactin
- Anti-Mullerian Hormone
- Estradiol
- Inhibin B

APPENDIX 3

IAAF-APPROVED SPECIALIST REFERENCE CENTRES

Center	Expert	Address
Stockholm (SWE)	Prof. Martin Ritzén	Dept. of Women's and Children's Health, Paediatric Endocrinology Karolinska Hospital Q2:08, Stockholm
	Prof. Angelica Lindén Hirshberg	Dept. of Women's and Children's Health, Division of Obstetrics & Gynecology Karolinska Hospital, Stockholm
Nice (FRA)	Prof. Patrick Fenichel	Service d'endocrinologie et médecine de la reproduction, Hôpital de l Archet, CHU de Nice, BP 3079, 06202 Nice cedex 03
Hershey, PA (USA)	Prof. Peter A Lee	Dept. Pediatrics, Penn State College of Medicine, Hershey, Pennsylvania
Melbourne (AUS)	Prof. Jeffrey D. Zajac	Dept. of Medicine, The University of Melbourne, Austin Health & Northern Health, Studley Road, Heidelberg, Victoria 3084, Melbourne
Tokyo (JAP)	Prof. Tsutomu ("Tom") Ogata	National Research Institute for Child Health and Development, Tokyo
Sao Paolo (BRA)	Prof. Berenice Mendonca	Unidade de Endocrinologia do Desenvolvimento e Laboratório de Hormônios e Genética Molecular, Disciplina de Endocrinologia, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Sao Paolo

APPENDIX 4

CONSENSUS STATEMENT ON MANAGEMENT OF INTERSEX DISORDERS

APPENDIX 5

Examples of Medical Conditions resulting in Hyperandrogenism

The following is a non-exhaustive list of examples of medical conditions resulting in hyperandrogenism:

Medical Condition
Congenital adrenal hyperplasia (CAH) 21-hydroxylase deficiency.
Congenital adrenal hyperplasia (CAH) 11β -hydroxylase deficiency
3β-hydroxysteroid dehydrogenase deficiency
5α-reductase type 2 deficiency
Androgen insensitivity syndrome (AIS)
Ovotesticular DSD (previously called “true hermaphroiditism”)
17β-hydroxysteroid dehydrogenase type 3 (17β- HSD3) deficiency
Polycystic ovary syndrome (PCOS)
Adrenal carcinoma
Luteoma of pregnancy