The new 5th WHO manual semen parameter reference values – do they help or hinder?

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ESHRE SIG-Andrology Campus Meeting
Thessaloniki, Greece
01 – 03 October 2009

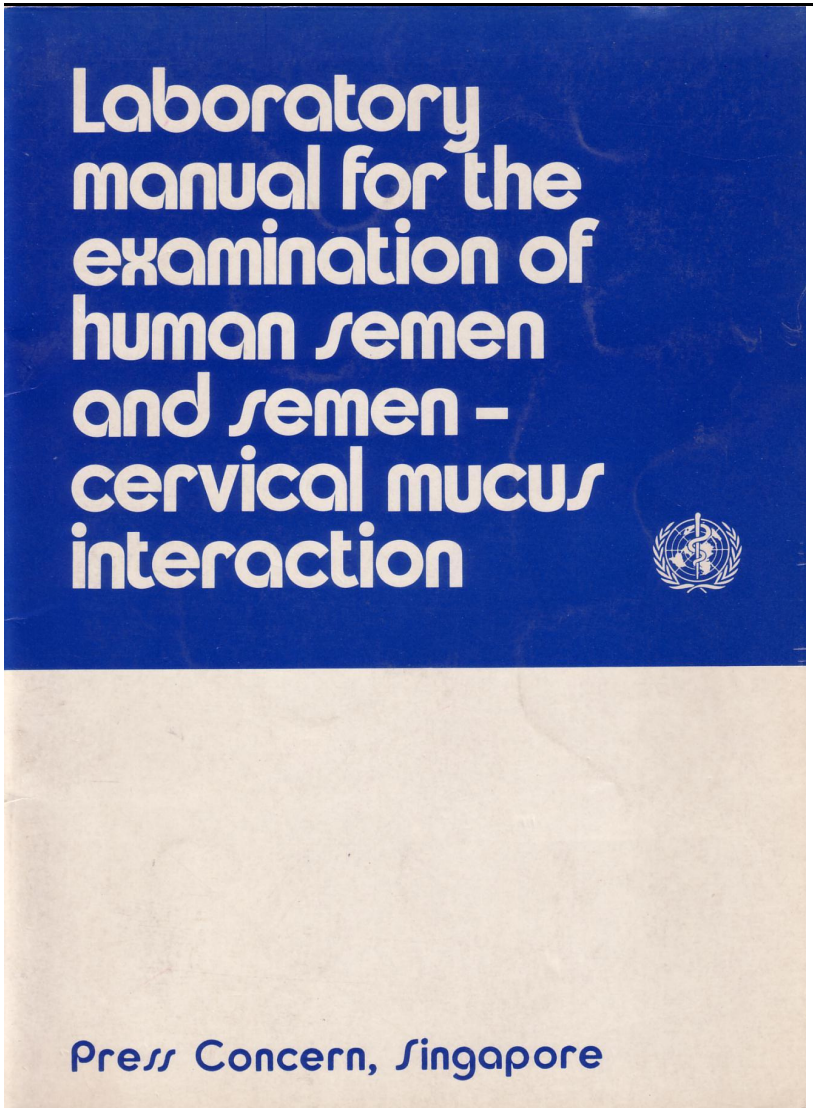
Disclosure

I have no commercial or other activities that may reflect on the contents of this lecture

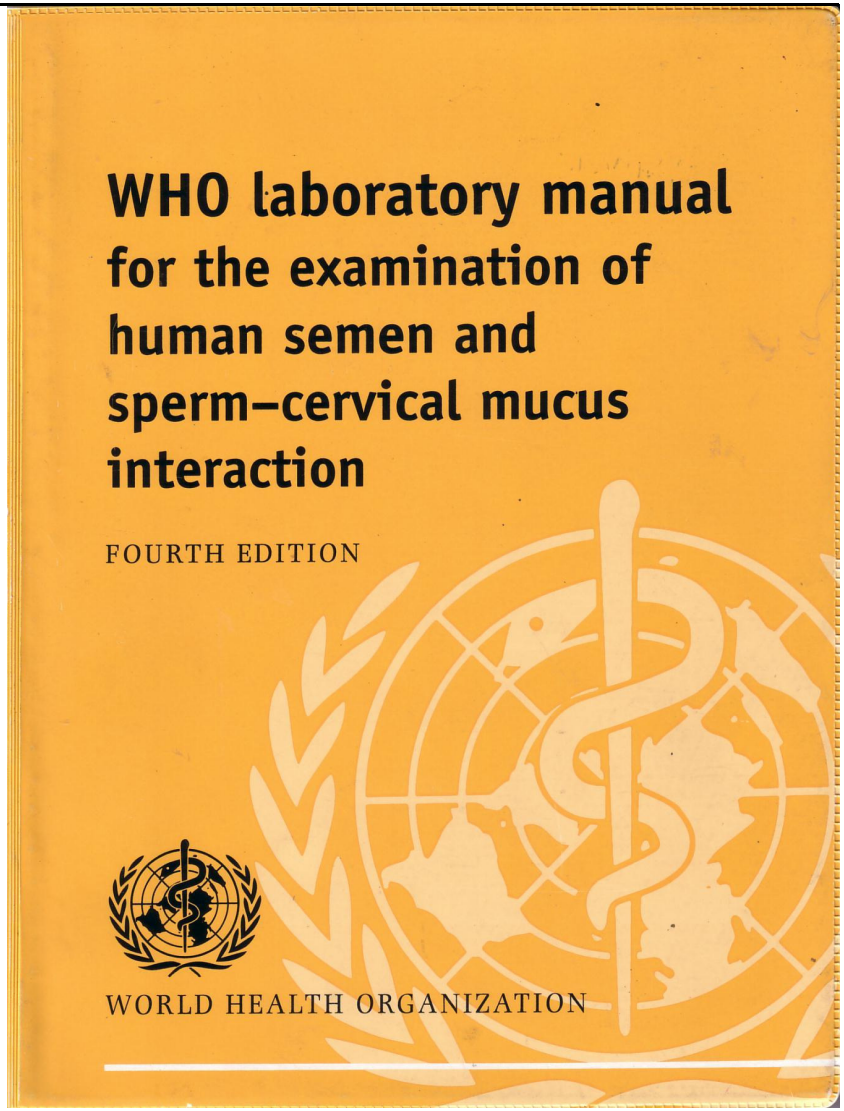
Lecture objectives

- Give an overview of the evolution of the (normal) semen parameter values of the different WHO manual editions from 1980 to 1999
- Discuss the expected new proposed values of the forthcoming 5th edition (2009/2010 ??)
- Discuss the usefulness of the expected new semen parameter values with special reference to normal sperm morphology

Evolution of the WHO manuals form the 1st edition of 1980 to the 4th edition of 1999



1980



1999

Old manuals

Old wording in previous manuals

- 1st edition
  - No specific wording or definitions for semen parameter values (Used normal and fertile range)
- 2nd and 3rd editions
  - Used term “normal” values
- 4th edition uses term “reference” values
  - Statement
    - The (mean?) normal “reference” values quoted are for “normal” men and NOT the MINIMUM requirements for fertilisation

Old manuals

- Quoted “normal or reference” values
  - Is a “hinder”
- Due to misinterpretations
  - Many persons interpreted men with values lower then quoted “normal” values as infertile
  - Making wrong diagnosis and prognosis
  - Leading to impropriate treatment

Expected changes in the new 5th edition

- New wording for definition of “normal” values
- Statements on aims and expectations
- Methods and materials
- New “normal” semen parameter values

Cooper, 2007 (ESHRE campus meeting)

New wording for definition of “normal” values in 5th WHO manual edition

- New wording for “normal of reference” values
  - Will refer to
    - Lower reference limits
    - Reference ranges

Aim and expectations of the new WHO manual (1)

- Aims
  - Increasing the accuracy of the analytical results
  - Providing more experimental details of common methods
  - Giving hints and details of what to do when QC results are poor

Cooper, 2007 (ESHRE campus meeting)

Aim and expectations of the new WHO manual (2)

- Expectations
  - To improve standardisation between laboratories
  - Improve diagnostic values of semen analyses results
  - Improve follow-up of therapeutic treatment

Cooper, 2007 (ESHRE campus meeting)

Material and methods for 5th edition (1)

- Reference population
  - Fathers (Couples with time to pregnancies of ≤ 12 months)
  - 1600+ couples
  - Five centres from 3 continents
- Samples
  - Only 1 sample per father
  - Complete sample after 3-7 days of abstinence

Cooper, 2007 (ESHRE campus meeting)

Material and methods for 5th edition (2)

- Methods
  - Only laboratories following WHO manual guidelines (IQC + EQC laboratories only)
  - Sperm concentration by haemocytometer only
  - Sperm morphology evaluation according to STRICT CRITERIA only
- Statistics
  - Reference values based on the lower 5th percentile limits

Cooper, 2007 (ESHRE campus meeting)

Comparison of new expected 5th WHO manual semen reference values

- To previous WHO manuals values
  - 2nd to 4th editions (1987 to 1999)
- To recent published values in the literature

Normal values for WHO manuals, editions 2- 4 and expected lower reference limits for WHO manual 5

Semen parameter	WHO edition and year			
	2nd - 1987	3rd - 1992	4th - 1999	**5th - 2009/10**
Volume (ml)	2.0	2.0	2.0	1.5
Sperm concentration (10^6/ml)	20	20	20	15
Total sperm count (10^6)	40	40	40	39
Motility (% progressive)	50	50	50	28
Vitality (% live)	50	75	75	59
Morphology (% normal)	50	30	(15)	3

Cooper, 2007 (ESHRE campus meeting)

Recent studies proposing new “cut-off, normal or reference” values

- Three types of literature studies
  - Based on
    - In vivo or in vitro pregnancies
    - Fertile versus subfertile populations
    - Lower interval values

In vivo or *in vitro* pregnancy studies

- Van Zyl et al., 1975, 1976, 1990, 2006
- Eggert-Kruse et al., 1996
- Zinaman et al., 2000

Fertile versus sub- or infertile populations

- Ombelet et al., 1997
- Günalp et al., 2001
- Menkveld et al., 2001
- Guzick et al., 2001

Lower percentile intervals

- Ombelet et al., 1997 - Lower 10th percentile
- Menkveld et al., 2001 - Lower 10th percentile
- Haugen et al., 2006 - Lower 10th and 5th percentile

Comparison of expected new WHO manual lower reference values and recent published values

Semen parameter	Publication			
	Menkveld et al., 2001*	Haugen et al., 2006		**5th WHO manual**
		5th	10th	
Sperm concentration (10^6/ml)	N/A	10.6	16.9	**15**
Motility (% progressive)	20	33	43	**28**
Morphology (% normal)	3	3	4	**3**

*Adjusted ROC curve values

Comments on expected new WHO manual lower reference values

- New expected WHO lower reference values are more or less in line with values of recent published literature
- New expected WHO lower reference values

Help or Hinder?

Not a great advantage/help for prediction of a males possible fertility potential

Comments on the expected lower reference values of new 5th edition

- Need a more “precise or detailed” breakdown of semen parameter values
- Need a new approach to interpretation of normal sperm morphology values

Need for a more “precise or detailed” breakdown of semen parameter values

Classification of male fertility potential according to semen parameters as used at Tygerberg Hospital

Semen parameter	Fertility potential classification		
	Infertile	Subfertile	Infertile
Concentration (10^6/ml)	< 2.0	2.0 – 9.9	≥ 10.0
Motility (% progressive)	< 10	10 – 29	≥ 30
Morphology (% normal)	< 5	5 - 14	≥ 15
Semen volume (ml)	< 1.0	> 6.0	1.0 – 6.0

Fertile = Optimal chance for pregnancy

Subfertile = Reduced chance for pregnancy

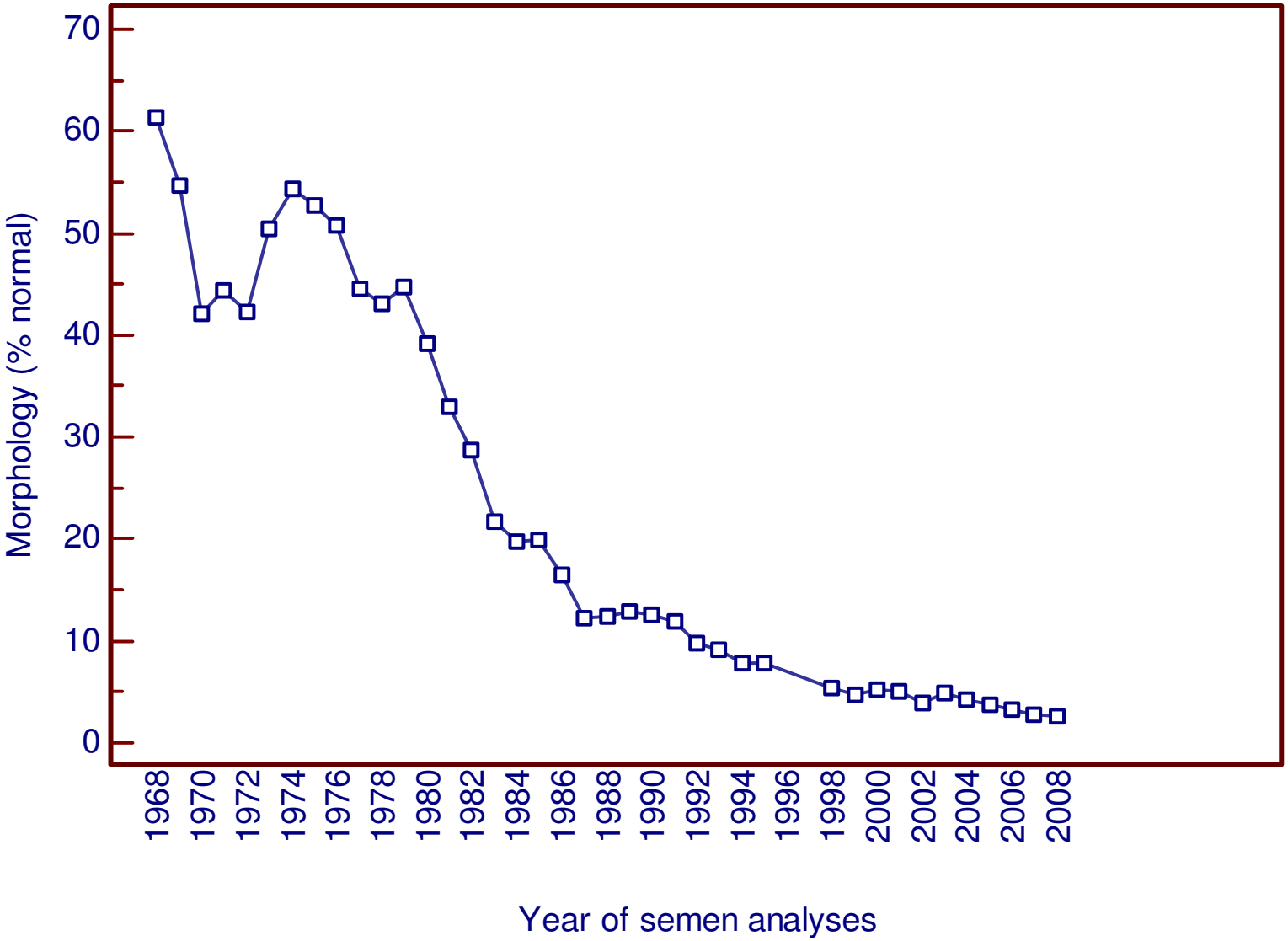
Infertile = Small change for pregnancy

Need for a new approach for the interpretation of normal sperm morphology values

Sperm morphology

- Values as used at Tygerberg hospital and according to the old editions of WHO manuals are not applicable anymore due to decrease in normal sperm morphology values over years
- Possible reasons for decline in normal sperm morphology parameters over years
- New approach for interpretation of sperm morphology parameters is needed

Overview of declining sperm morphology values over years



Menkveld etal., 1986; Menkveld, 2009

Examples of declining sperm morphology values form the literature (1) Distribution of normal morphology – Van Zyl study - 1972

Morphology interval (%)	Number of men	Percentage
0 – 10	0	0.0
11 – 20	4	3.2
21 – 30	9	7.1
31 – 40	24	19.0
41 – 50	23	18.3
51 – 60	28	22.2
61 – 70	19	15.1
71 – 80	11	8.7
81 – 90	6	4.8
91 – 100	2	1.6
Total	190	100.0

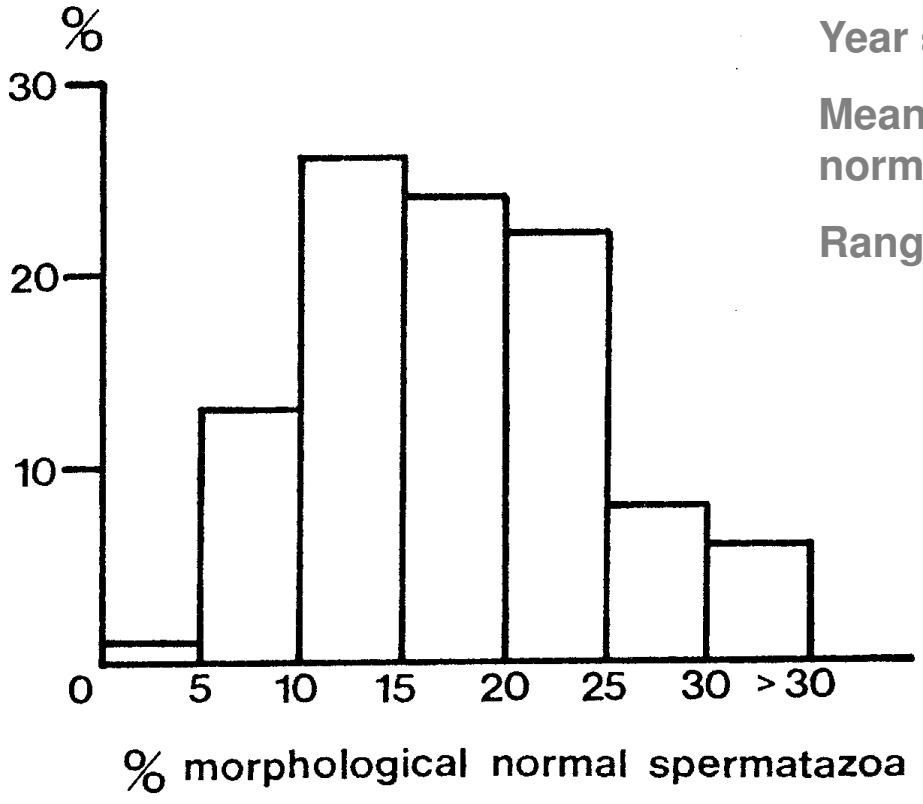
Van Zyl, S Afr J Obstet Gynaec 10:17-23,1972

Examples of declining sperm morphology values form the literature (2) Distribution of normal morphology – Kruger et al., 1986

Morphology interval (%)	Number of men	Percentage
0 – 14	22	11.6
15 – 30	83	43.2
31 – 45	67	35.2
45 – 60	18	9.5
Total	190	100.0

Kruger et al., al., Fertil Steril 46:1118-23,1986

Examples of declining sperm morphology values form the literature (3) – Frequency distribution of percentage morphological normal spermatozoa in a population of men referred for IVF treatment (n = 106)



Year = 1990

Mean = 16.7 ± 7.6% normal

Range = 3 – 41% normal

Menkveld et al., Hum Reprod 5:586-92,1990

Declining sperm morphology values

- Decline due to three possible reasons
  - Stricter application of evaluation criteria
  - Negative environmental influences
  - Additional parameters for sperm morphology abnormalities

Stricter application of sperm morphology evaluation criteria

- Introduction of STRICT CRITERIA
  - Strict versus liberal approach
    - Chanced from borderline spermatozoa previous regarded as normal to TOO BE REGARDED AS ABNORMAL
  - Over critical approach for interpretation of normal
  - Inadequate training

Negative environmental influences

- Exposure to pseudo-estrogens of mother, unborn baby and male
  - Higher incidences of decrease in male reproductive health
- Higher exposure to toxic environment and occupation hasards
  - Decrease in spermatogenesis and lower/poorer semen parameters
- Higher incidences of sexual transmitted diseases
  - Lower semen parameters
  - Increase of leukocytospermia
  - Increased sperm DNA damage

Decline due to introduction of additional parameters for sperm morphology abnormalities

- For example
  - Differential classification of acrosome morphology
    - Normal
    - Staining defects
    - Too large
    - Too small
    - Other/Amorphous

New approach for interpretation of sperm morphology parameters is needed

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- Better use of existing sperm morphology parameters
- Better quality control
- Use of additional sperm morphology parameter, especially in patients with teratozoospermia according new lower reference value of ≤ 3% (Poor prognosis group)

Better use of existing sperm morphology parameters

- Acrosome morphology (Acrosome index)
  - TZI
  - Cytoplasmic residues
  - Semen cytology
    - Identification, reporting and treatment of WBC on semen smears

Better quality control for sperm morphology evaluation

Problem

- Lack of intra and interlaboratory quality control
- Lack off standardisation between different international QC schemes

Solutions

- Betters adherence to WHO guidelines (aim of new WHO manual)
- Better co-operation between and standardisation of the different international QC schemes

Use of additional sperm morphology parameters

In poor prognosis group (≤ 3%)

- Identification of abnormal sperm morphology patterns
  - Abnormal acrosome staining
  - Large sperm/acrosome patterns
  - Small sperm/acrosome patterns
  - Elongated sperm morphology patterns


Abnormal acrosome staining

Large spermatozoa/large acrosomes


Small spermatozoa/acrosomes

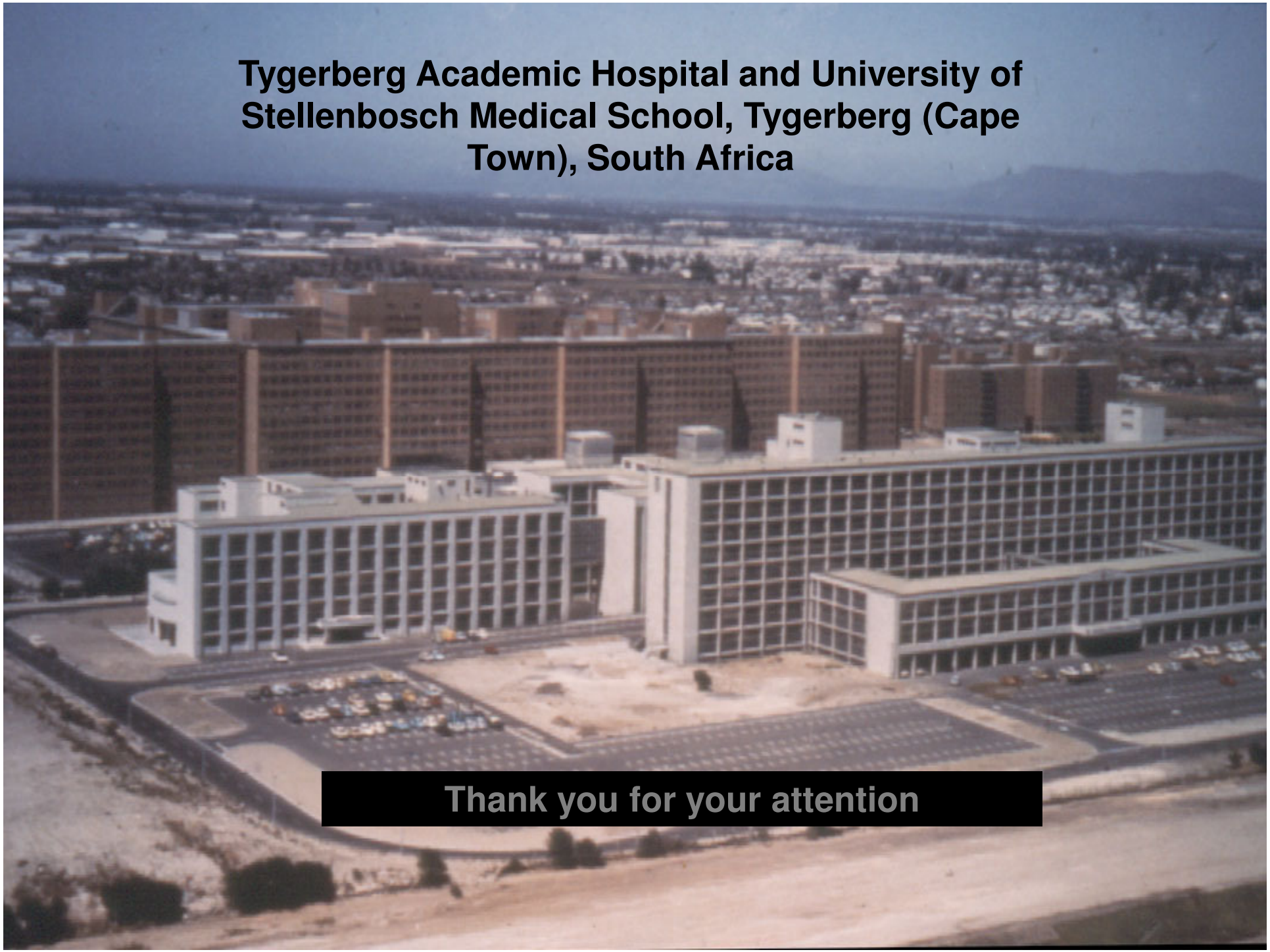
Conclusions (1)

- Expected new semen parameter values of soon to released 5th edition of the WHO manual
  - Not expected to be of increased help in diagnosis of male fertility potential
  - Expect very low normal sperm morphology normal reference value of ≤ 3%
  - Need to be aware of ongoing decrease in normal sperm morphology values

Conclusions (2)

For solving problem of expected very low normal sperm morphology value and ongoing decrease in normal sperm morphology values

- Need more in-depth sperm morphology evaluation parameters
- Need better intra- and inter-laboratory QC for sperm morphology evaluation criteria
- Standardisation of international QC schemes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Thank you for your attention

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