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# The Use of Colposcopy in Microbicide Trials

# What is colposcopy?

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Key features:

- Magnification

- Good light source

Generally used to evaluate cervix

Increasingly used to evaluate effects  
of new products on genital tract



# Colposcopy for neoplasia vs evaluation of new vaginal products

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- ◆ Neoplasia:
  - ▶ Type of finding: precancerous conditions
  - ▶ Area studied: usually cervix
- ◆ Microbicide safety
  - ▶ Type of finding: Disruption of epithelium and blood vessels, and color change
  - ▶ Areas studied: Cervix, vagina, external genitalia

# Vaginal colposcopy – not new

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- ◆ 1965 - Diagnosis of trichomonas
- ◆ 1966 - Diagnosis of vaginal dysplasia
- ◆ 1967 - Effect of ovulation inhibitors
- ◆ 1968 - Vaginal trauma
- ◆ 1974 - Vaginal adenosis in DES daughters
- ◆ 1976 - Condylomata
- ◆ 1977 - Normal canine vaginal cytology
- ◆ 1980 - Tampons
- ◆ 1983 - Vaginal ulcerations in Toxic Shock
- ◆ 1989 - Effect of hormones

# Vaginal colposcopy – its use in evaluating vaginal products is new

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- ◆ 1991 - Female condom
- ◆ 1991 – N-9 supps
- ◆ 1993 - Vaginal rings, N-9 supps
- ◆ 1995 – Menfegol. \* WHO MANUAL PUBLISHED \*
- ◆ 1996 - N9-lubricated condoms, N-9 gel, N-9 sponge
- ◆ 1997 - Dextrin sulfate, BZK film, carrageenan, N-9 gel, N-9 film
- ◆ 1998 –N-9 gel, N-9 film
- ◆ 1999 - Healthy women, N-9 film, N-9 gel
- ◆ 2000 –N-9 gel \* WHO/CONRAD UPDATE PUBLISHED\*
- ◆ 2001 –N-9 gel

# Current procedure

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- ◆ Position patient
- ◆ Examine external genitalia
- ◆ Insert speculum
- ◆ Perform naked eye exam
- ◆ Perform wet prep if needed
- ◆ Lavage
- ◆ Examine cervix
- ◆ Examine fornices
- ◆ Examine vaginal walls

# Current nomenclature

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- ◆ Epithelium:
  - ▶ Integrity:
    - Intact
    - Not intact:
      - Deep disruption
      - Superficial disruption
  - ▶ Color:
    - Normal
    - Slightly red, red, white, other (including pale)
- ◆ Blood vessels:
  - ▶ Integrity:
    - Intact
    - Not intact

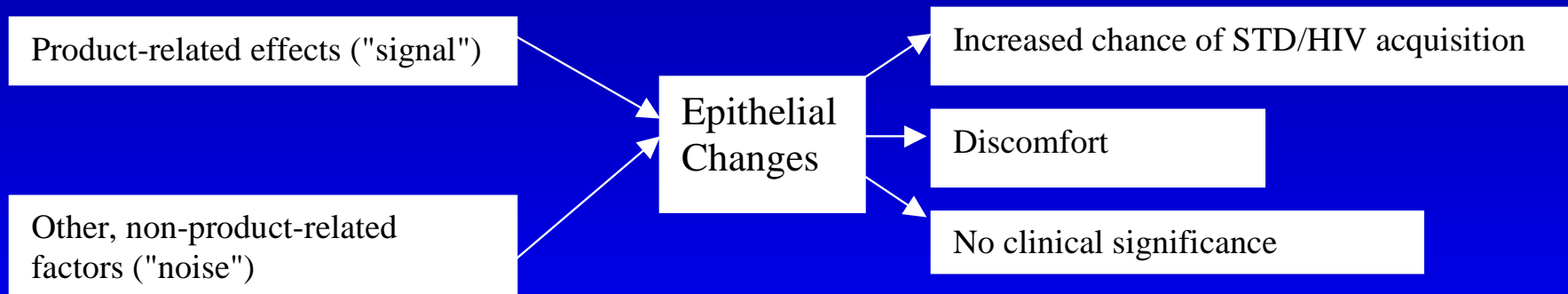
# Use of terms

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- ◆ E.g. petechiae, edema, etc
- ◆ Good for communicating and double-checking data
- ◆ Status of epithelium and blood vessels better for statistical analysis

# Why use colposcopy for new vaginal product research?

Possible scenario:



# Where does colposcopy fit in?

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- ◆ May be able to detect epithelial changes better than:
  - ▶ Naked eye exam
    - In Fraser study,\* 80% of findings were seen clearly only with colposcope
  - ▶ Symptoms
    - In many studies, symptoms do not correlate with colposcopy
  - ▶ Biopsy
    - In many studies, biopsy does not correlate with colposcopy
  - ▶ Studies of inflammatory markers
    - Being studied

\*Fraser, Hum Reprod. 1999 Aug;14(8):1974-8

# Problems with colposcopy

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- ◆ Differences in what is felt to be recordable
  - ▶ By different examiners
  - ▶ At different exams
  - ▶ At different times in exam
- ◆ “Too much” data: type of finding, color, location, size → hard to compare products
- ◆ Not clear what is important:
  - ▶ Is 1 woman with 100 findings “worse” than 100 women with 1 finding each?
  - ▶ Are two findings of 1 cm<sup>2</sup> “worse” than 1 finding of 2 cm<sup>2</sup>?

# CONRAD study in analysis

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- ◆ Objectives:
  - ▶ Compare two observers
  - ▶ Look at effect of the exam itself
  - ▶ Compare naked eye with colposcope
  - ▶ Compare colposcope with Aviscope
  - ▶ Compare 35 mm photos with digital images
  - ▶ Compare inflammatory markers with colposcopic findings

# Colposcopy does not answer:

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- ◆ How do we know that the vaginal product being studied caused the finding being seen?
- ◆ Does the finding being seen predispose to HIV/ other STDs?

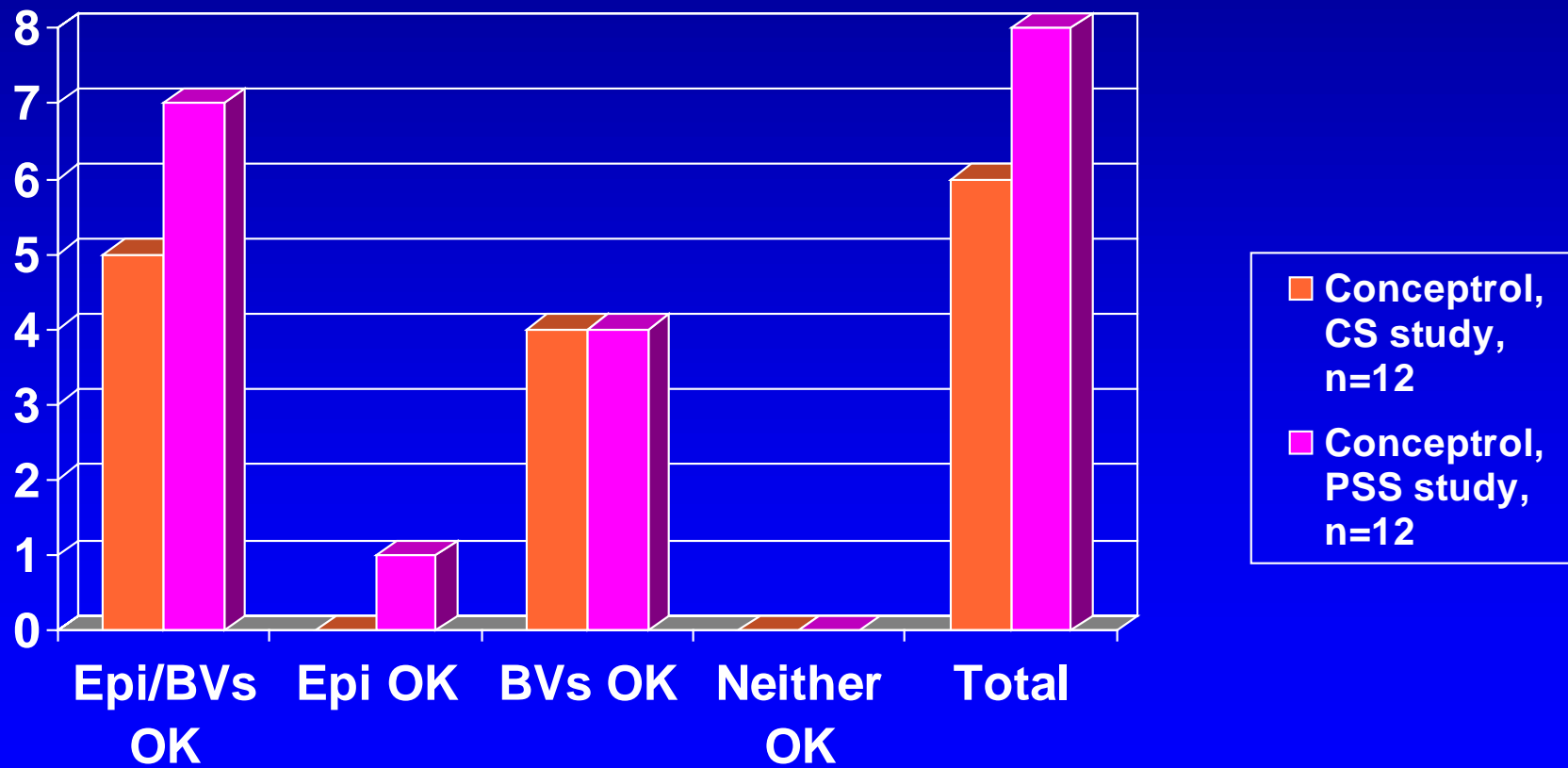
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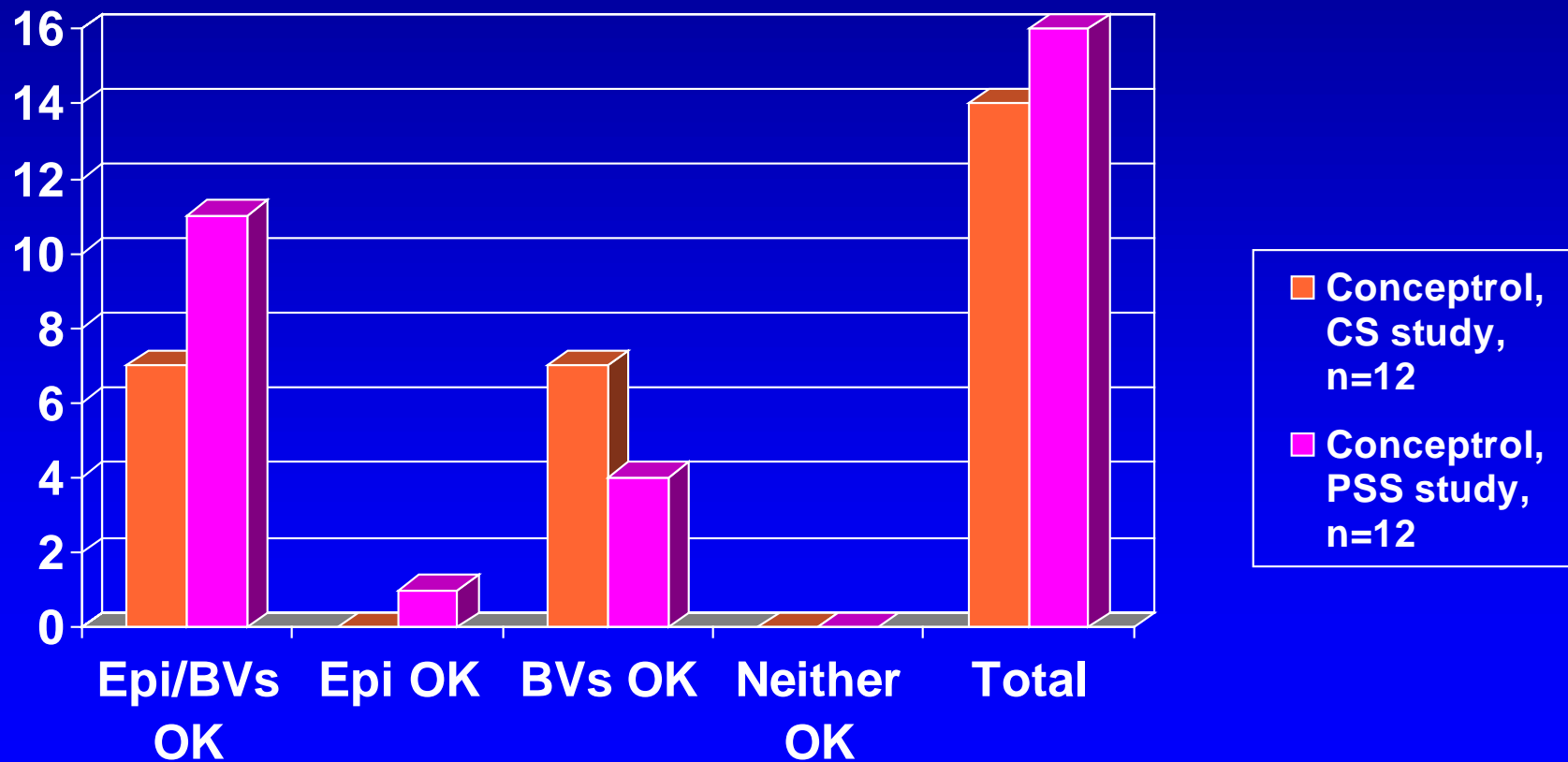
- ◆ Findings exist without the use of products\*
- ◆ Findings seen in published studies on N-9:
  - ▶ Some but not all studies found an increase in colposcopic findings among N-9 users
    - Pattern of more findings with increasing dose or frequency of use
    - Fairly consistent results in 2 CONRAD studies

\*Fraser, Hum Reprod. 1999 Aug;14(8):1974-8, and Van Damme, AIDS, 1998 12:433-437

# Conceptrol<sup>®</sup> results from 2 different CONRAD studies, # of women w/ findings



# Conceptrol results from 2 different CONRAD studies, # of findings



# Does the finding being seen predispose to HIV/other STDs?

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- ◆ Plummer 1991:
  - ▶ Ulcers & HIV: OR 3.3 (95% CI 1.2-10.1)
- ◆ Kreiss 1992:
  - ▶ Ulcers at enrollment & HIV: HR 2.3 (95% CI 1.0,5.2)
- ◆ Weir 1995:
  - ▶ Ulcers during exposure & HIV: OR 1.1 (95% CI 0.3, 3.5)
- ◆ Roddy 1998:
  - ▶ "Genital lesions did not predict seroconversions"
- ◆ COL-1492 study:
  - ▶ Cannot pinpoint time of seroconversion or status of epithelium at that time

# Summary, current state of knowledge

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- ◆ Most studies of N-9 show colposcopic findings
- ◆ Women not using products have colposcopic findings
- ◆ Colposcopy can detect findings not seen with the naked eye and colposcopic findings do not correlate with symptoms and biopsy findings
- ◆ We do not know that colposcopically detected findings predispose to HIV/STDs
- ◆ Given these questions, is it ethical/efficient to use colposcopy?

## In my opinion.....



- ◆ Include colposcopy in studies until we know whether:
  - ▶ Colposcopically detected findings are of importance; and
  - ▶ Colposcopy picks up findings better than other methods

# Other opinions to consider....

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- ◆ FDA has no set guidelines
  - ▶ Would like to see colposcopy in Phase I and II and in subset of Phase III but is flexible
  - ▶ IWGM has similar position
- ◆ Utility:
  - ▶ Phase I :  
Microbicide---> epithelial changes---> HIV/STDs  
seen on colpo
  - ▶ Phase II/III :  
Microbicide---> epithelial changes---> HIV/STDs  
seen on colpo

# Efforts to standardize colposcopy

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- ◆ Uniform procedure and nomenclature
  - ▶ WHO manual 1995
  - ▶ Revised: "Update 2000" \*
  - ▶ Future update?
- ◆ Use of digital colposcopy and central reading
- ◆ Colposcopy atlas
  - ▶ Peter Kilmarx's group in Chang Rai
- ◆ Colposcopy training in Norfolk
  - ▶ GMP trials
  - ▶ HPTN trials

\* Available at [www.conrad.org](http://www.conrad.org) and in AIDS 2000 Oct 20;14(15):2221-7

# Follow-up workshop on colposcopy

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- ◆ First one in January 1999
- ◆ Next one in September 2003
- ◆ Goal: Review & make recommendations regarding methodologies for assessing vaginal epithelium:
  - Colposcopy
  - Lavage for inflammatory markers
  - Biopsy
  - Other