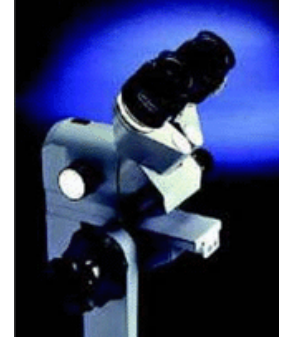


Colposcopy



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Evaluating Safety

How do we evaluate the safety of candidate microbicides?

- Systemic safety
 - AE's, lab values, exam, etc.
- Local safety
 - AE's, flora changes, exam, etc.
 - **Colposcopy**

Colposcopy

- Standard for safety assessment of vaginal products
- Goal = detection of epithelial changes that *may* increase the likelihood of acquisition of HIV or other STI
- Generally accepted reference is the WHO/CONRAD Manual



C | O | N | R | A | D

History

- 1995
 - WHO meeting
 - "Manual for the Standardization of Colposcopy for the Evaluation of Vaginally Administered Products"
- 1999
 - Revised in conjunction with expert review convened by CONRAD and WHO
 - "Update 2000"
- 2003
 - Third conference of experts
 - "Update 2004"



Epithelial Changes

- Hypothesis: Epithelial changes increase risk of infection
- Epithelial Changes
 - breaks in the epithelium
 - inflammation
 - other not well-characterized changes
- Multiple Causes

What Do Epithelial Changes Mean?

Epithelial changes could ...

- lead to an increased risk of STI, including HIV, **or**
- cause discomfort without increasing the risk of infection, **or**
- be of no clinical significance!!!

Minor vs. Significant Lesions

MINOR

- peeling
- ecchymosis
- petechiae
- erythema
- acetowhite lesion
- non-acetowhite lesion

SIGNIFICANT

- full thickness epithelial disruption
- abrasion
- laceration
- ulceration
- subepithelial hemorrhage with edema

Normal Cervix

Mucosa

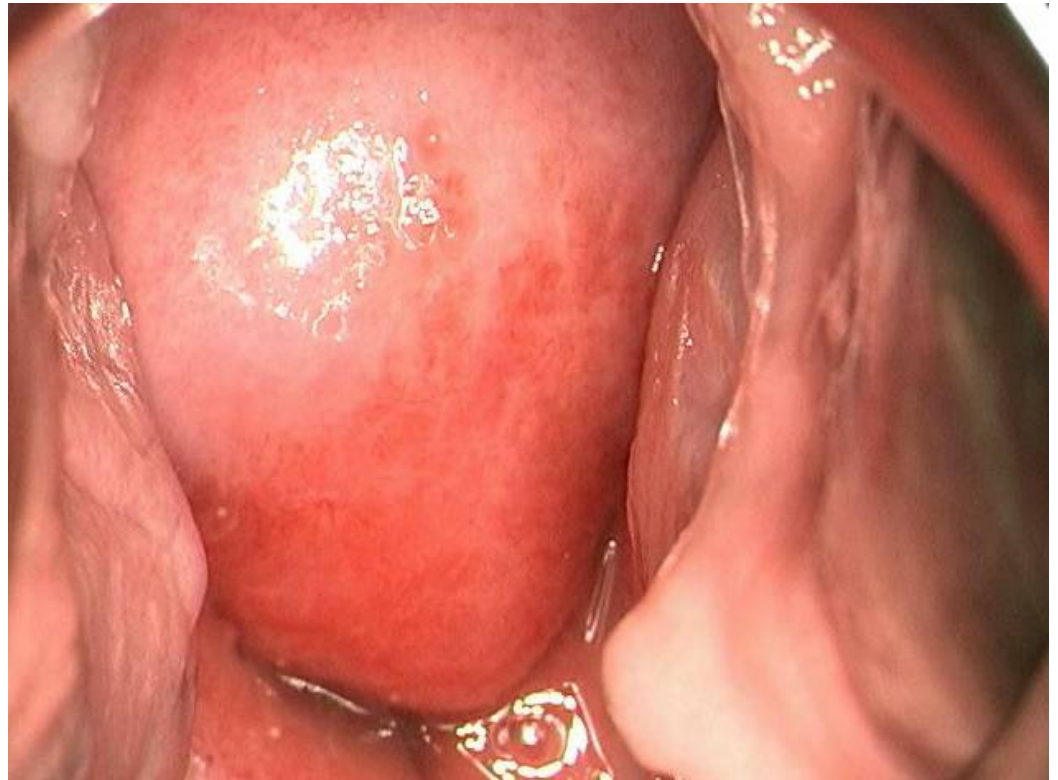
- Typically uniformly pink
- Epithelium intact
- Vessels intact



Erythema

Reddened areas

- Margins may or may not be clearly defined
- Epithelium intact
- Vessels intact



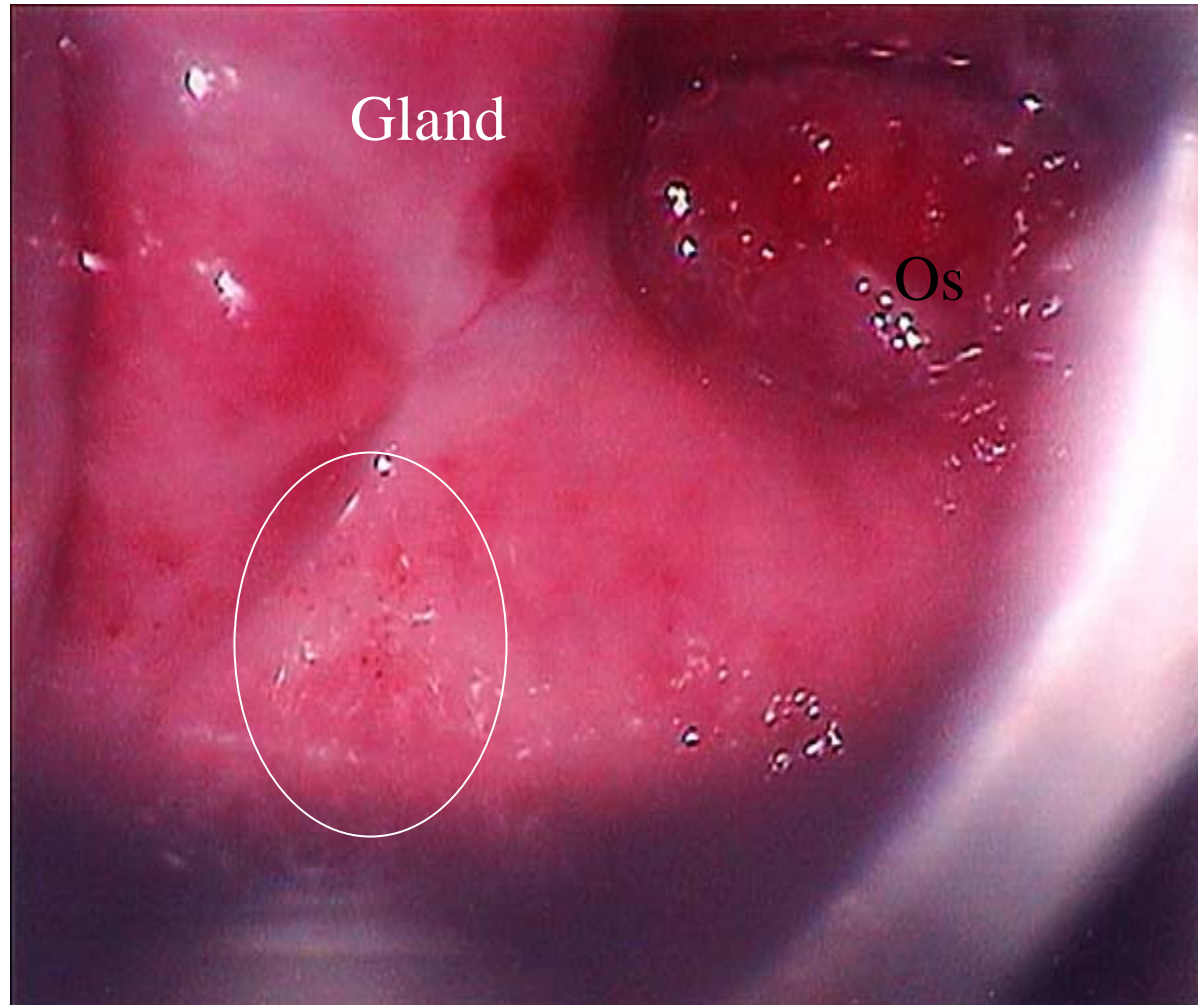
Edema

- Epithelium
 - Intact
 - Swollen
- Vessels
 - Intact
- Color:
normal or
pale



Petechiae

- Individual or group
- Epithelium intact
- Vessels disrupted
- $\leq 3\text{mm}$

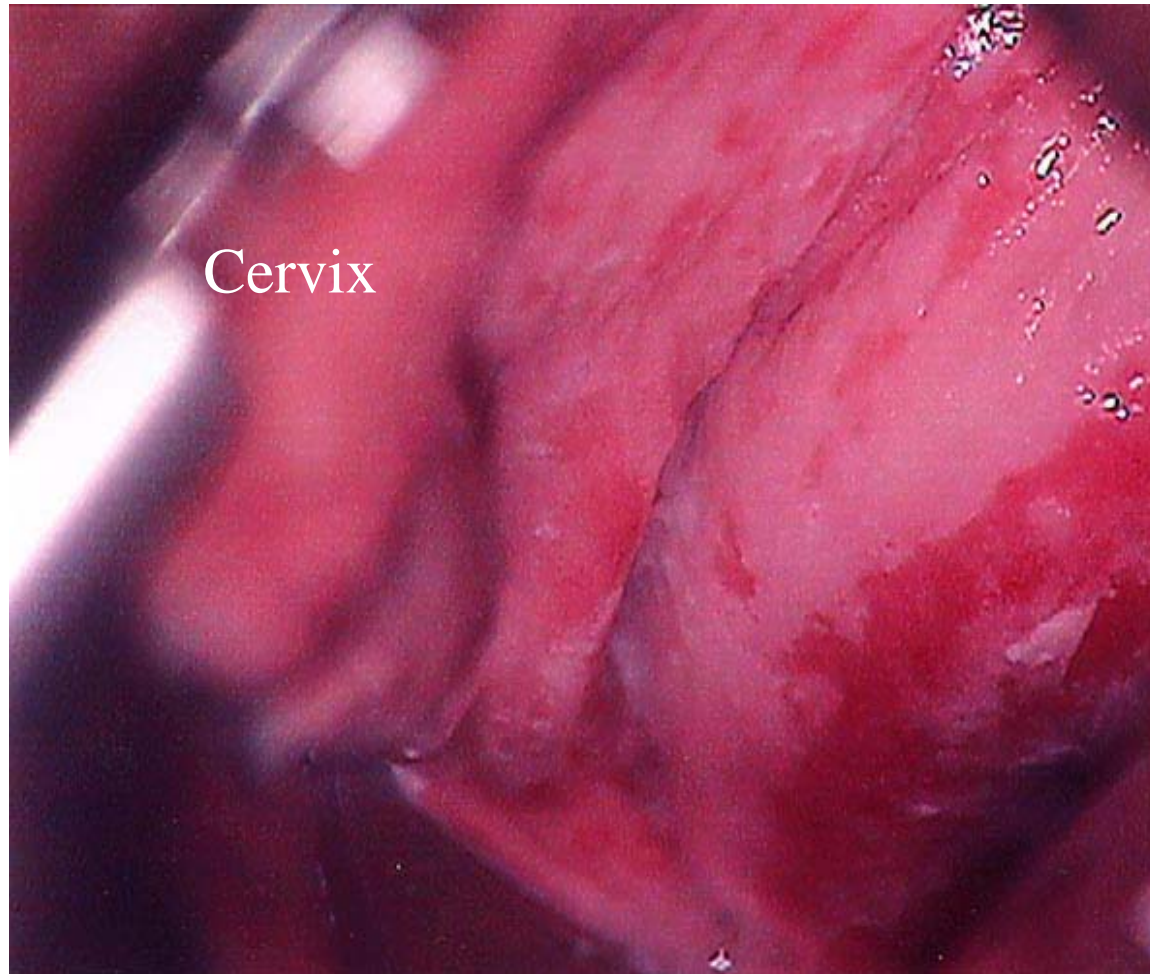


Ecchymosis

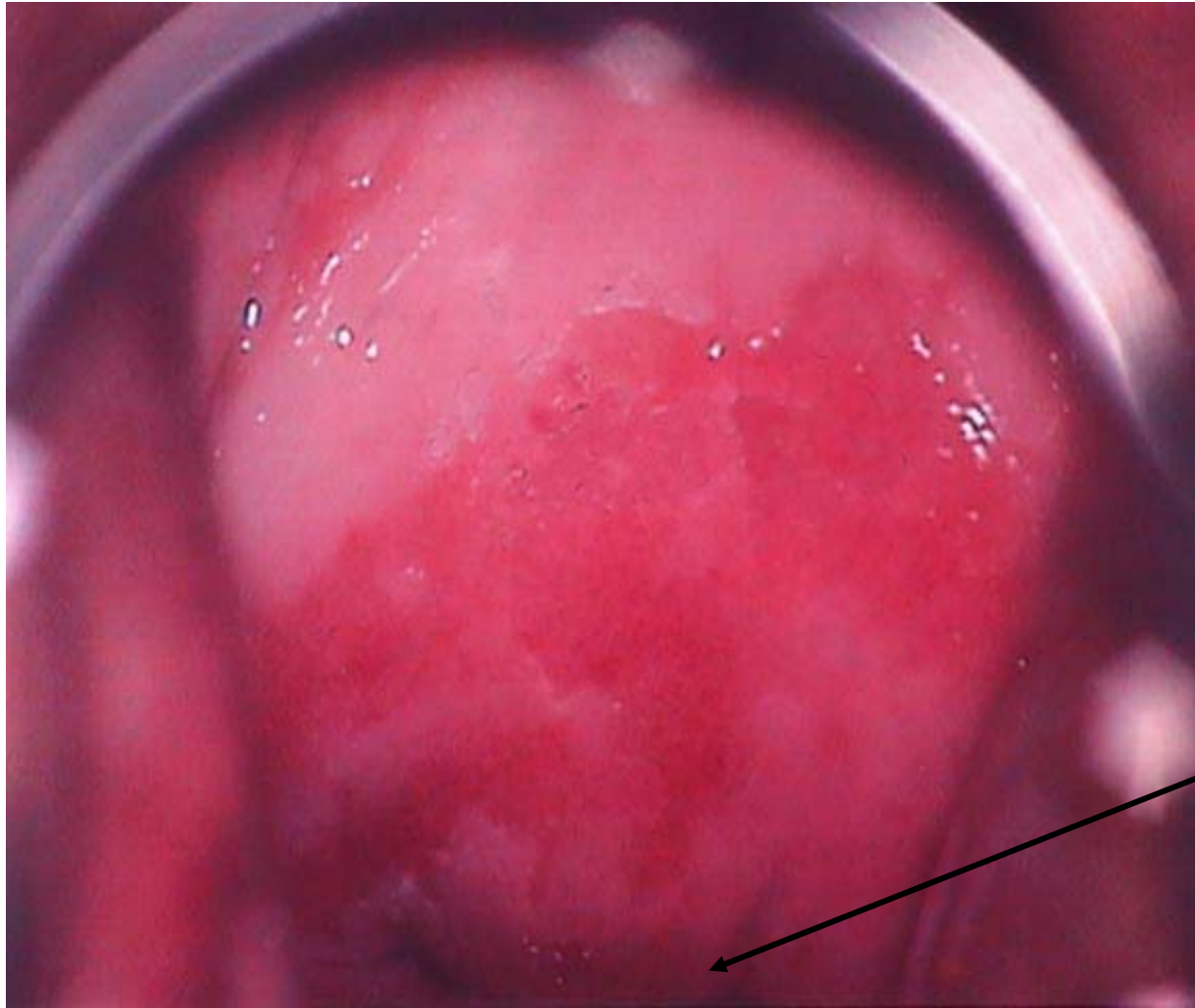
- Epithelium intact
- Vessels disrupted
- **>3mm**
- Color is red or purple



Peeling of Vagina



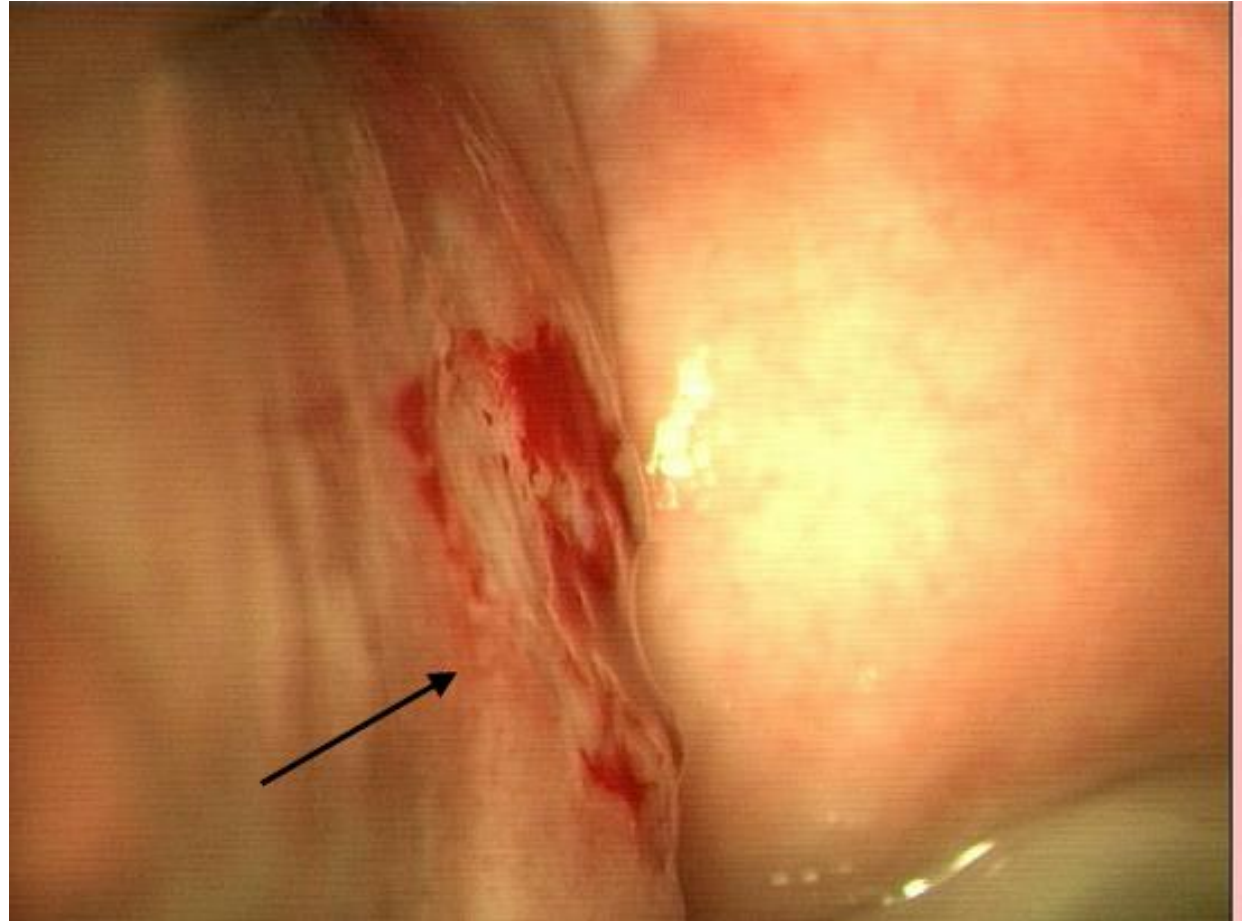
Peeling of Cervix



Cervical Os

Abrasion

- Epithelium disrupted (superficial or deep)
- Vessels disrupted
- Diffuse or poorly demarcated outline



Laceration

- Epithelium disrupted (superficial or deep)
- Vessels intact or disrupted
- Sharply demarcated linear finding
- Fissures appear to be linear “pulling apart” or wearing away of tissue
- Lacerations appear to be from trauma





Limitations of Colposcopy

- Requires: reliable electricity, expensive equipment, specific training
- Variation between observers
- Large number of observations
but...which ones are important when evaluating safety



Training

- Different evaluation than for dysplasia
 - Manipulation
 - Angles
 - Recording
- 3-6 months of proctoring

Variations between observers

- 14 subjects, 2 observers
- 5 paired examinations
- No product use
- Colposcopic examination averaged 7 min.
- More findings with magnification than naked eye (both major and minor lesions).
- Moderate agreement between examiners.

Baseline lesions: types

	Total (N=569)	Hormonal contraception (n=153)	Nonhormonal contraception (n=416)
Edema	0	0	0
Erythema	119 (36.1%)	27 (35.5%)	92 (36.2%)
Petechiae	143 (43.3%)	29 (38.2%)	114 (44.9%)
Ecchymosis	32 (9.7%)	4 (5.3%)	28 (11.0%)
Peeling*	19 (5.8%)	9 (11.8%)	10 (3.9%)
Ulceration	0	0	0
Abrasion	12 (3.6%)	4 (5.3%)	8 (3.2%)
Laceration	5 (1.5%)	3 (3.9%)	2 (0.8%)
Total no. lesions	330	76	254
Participants with lesion	197 (34.6%)	52 (34.0%)	145 (34.9%)

* p=0.02

O'Neill E, et al. Contraception 2008 (in press).

Baseline lesions: location

	Total (n=330)	Hormonal contraception (n=76)	Nonhormonal contraception (n=254)
Cervix	239 (72.4%)	55 (72.4%)	184 (72.5%)
Vaginal fornix	37 (11.2%)	8 (10.5%)	29 (11.4%)
Vaginal wall	19 (5.8%)	4 (5.3%)	15 (5.9%)
External genitalia	35 (10.6%)	9 (11.8%)	26 (10.2%)

Summary

- ❑ Colposcopy is an unvalidated standard
- ❑ Colposcopy finds more lesions
- ❑ Some naked eye lesions shown to be normal with colposcopy
- ❑ Many lesions are present without product use
- ❑ High cost colposcopy not proven with product use

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