



EMBRYOLOGIC BASIS OF FEMALE CONGENITAL TRACT MALFORMATIONS

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Congenital uterine anomalies and reproductive
outcome.

ESHRE Campus 2009

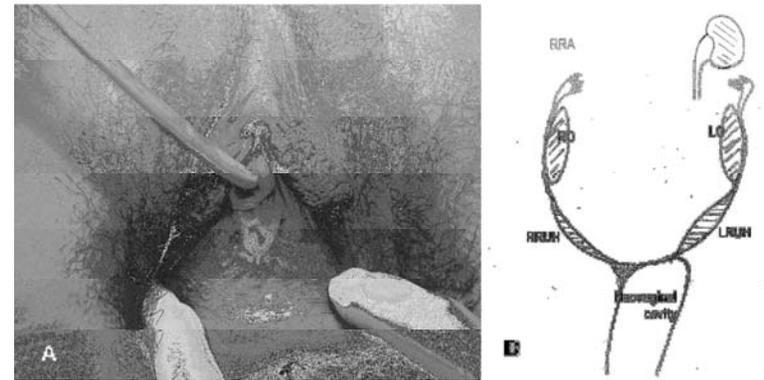
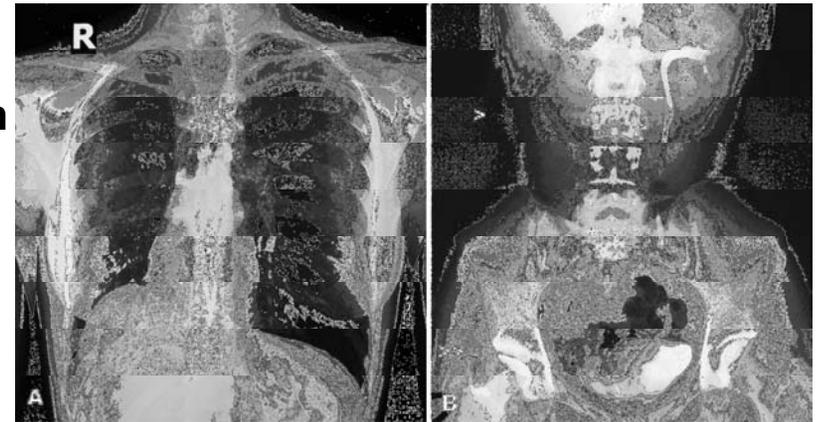
Manchester, United Kingdom, 20-21 November 2009

The direct cause of genital malformations is unknown

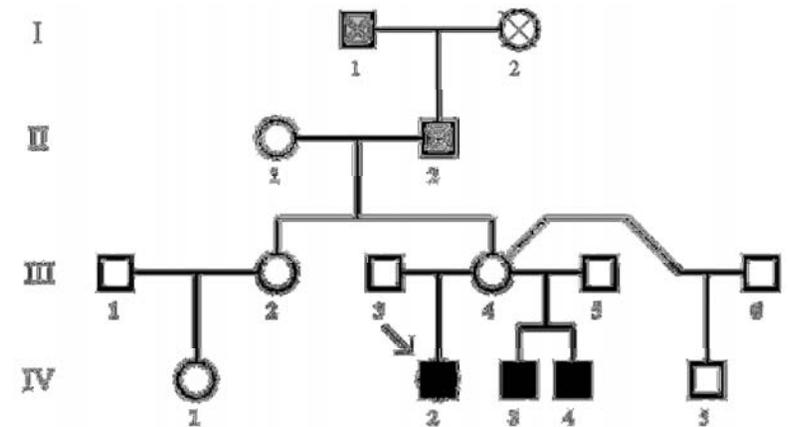
Sometimes:

- MURCS association
- Pulmonary hypoplasia, hereditary renal adysplasia, and Rokitansky syndrome (Figure).
- Others

- Multifactorial, poligenic, familiar mechanisms



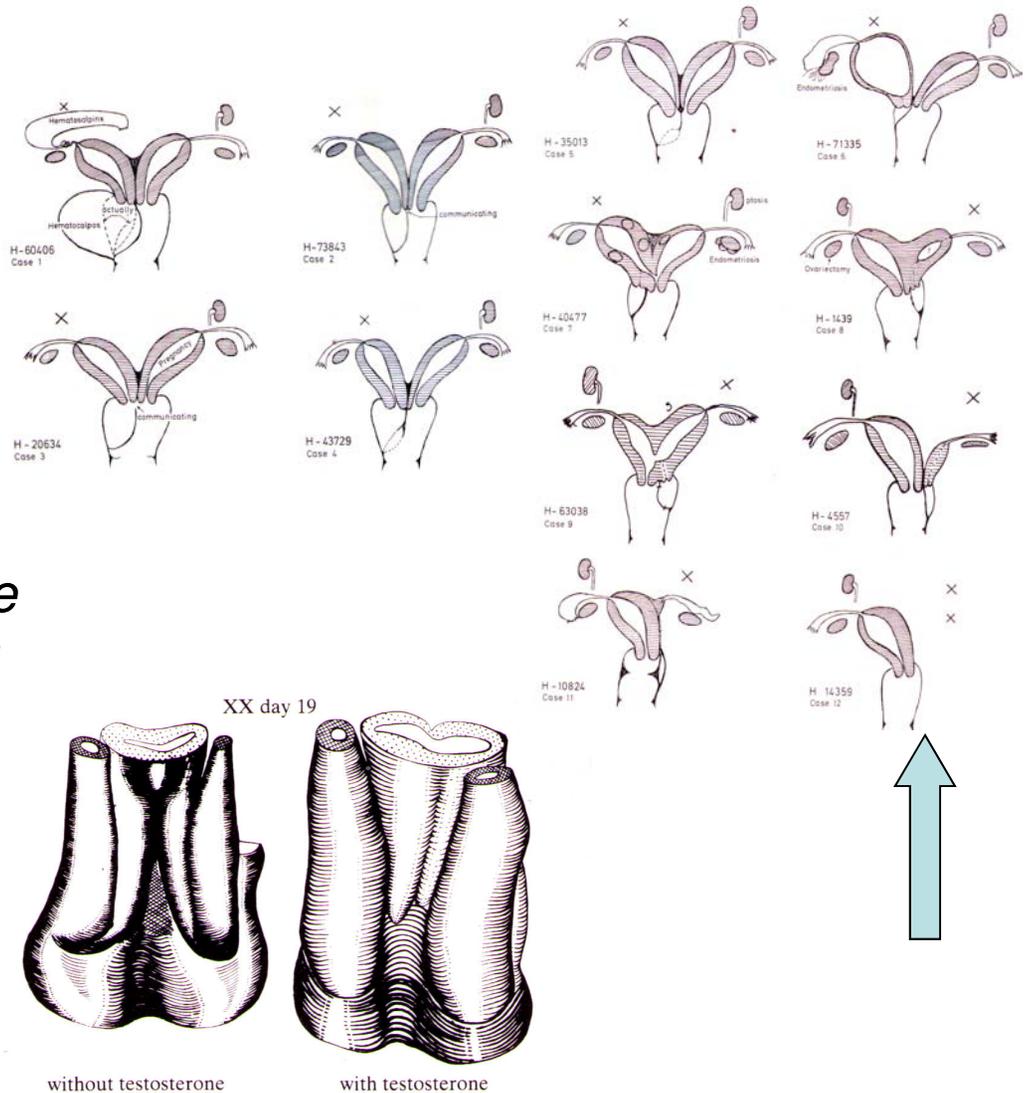
-  Pulmonary hypoplasia
-  Index case
-  Renal agenesis

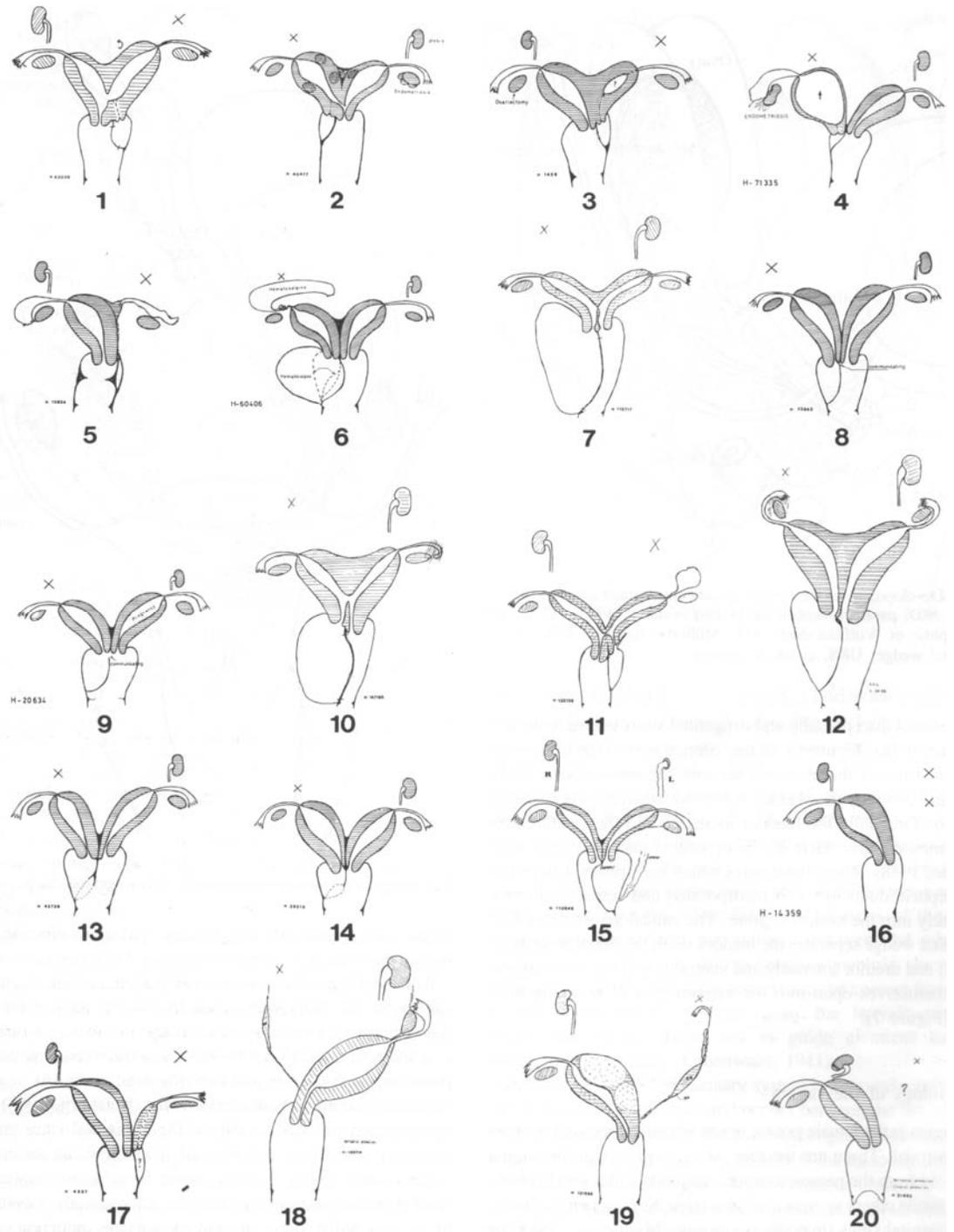
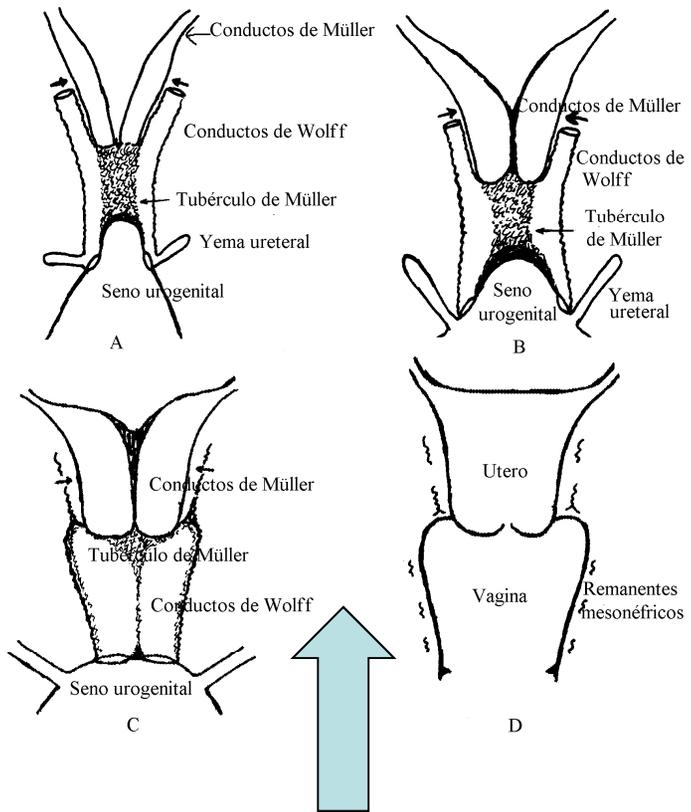


Family pedigree

The embryological development and the chain of anatomical events leading to malformation are better known

- Cases with double uterus associated with an obstructed hemivagina and ipsilateral renal agenesis.
- Acién et al. *Unilateral renal agenesis associated with ipsilateral blind hemivagina.* Arch Gynecol 1987;240:1-8
- Bok and Drews. *The role of the Wolffian ducts in the formation of the sinus vagina: an organ culture study.* J Embryol Exp Morphol 1983; 73:275-295

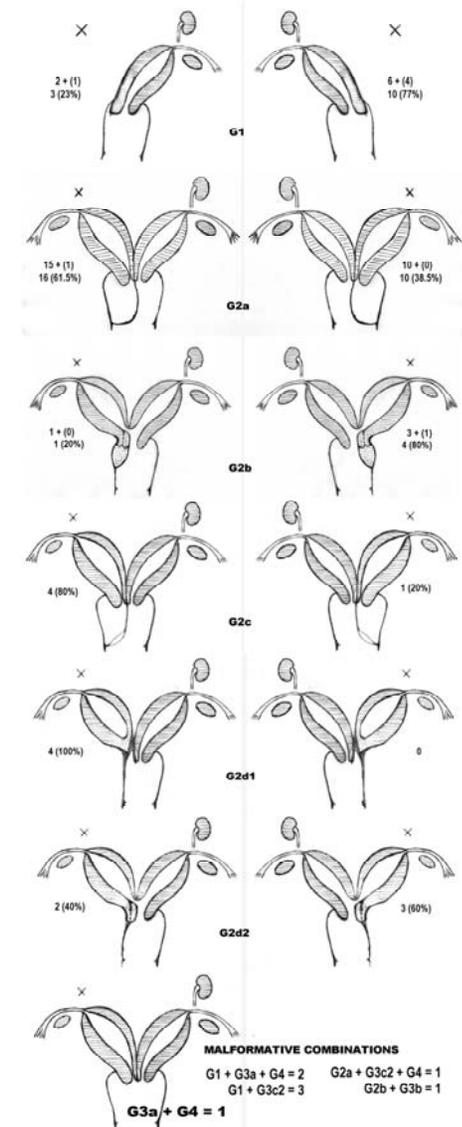




Acién P.
*Embryological observations
 on the female genital tract.*
 Hum Reprod 7:437-445, 1992

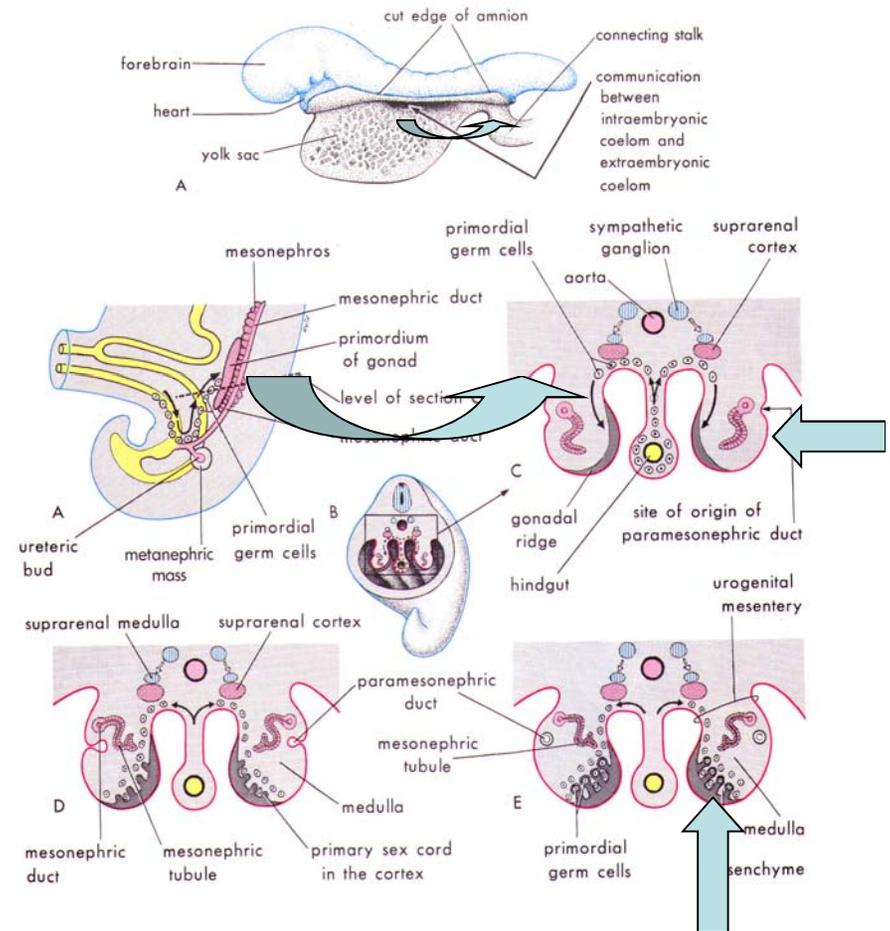
All cases of unilateral renal agenesis are associated either:

- 1. With **agenesis of all derivatives of the ipsilateral urogenital ridge** (generally with *unicornuate uterus* on the contralateral side) or
- 2. With **distal mesonephric anomalies** (generally with ipsilateral blind hemivagina) and uterine duplicity (*didelphys* or *bicornuate uterus*)



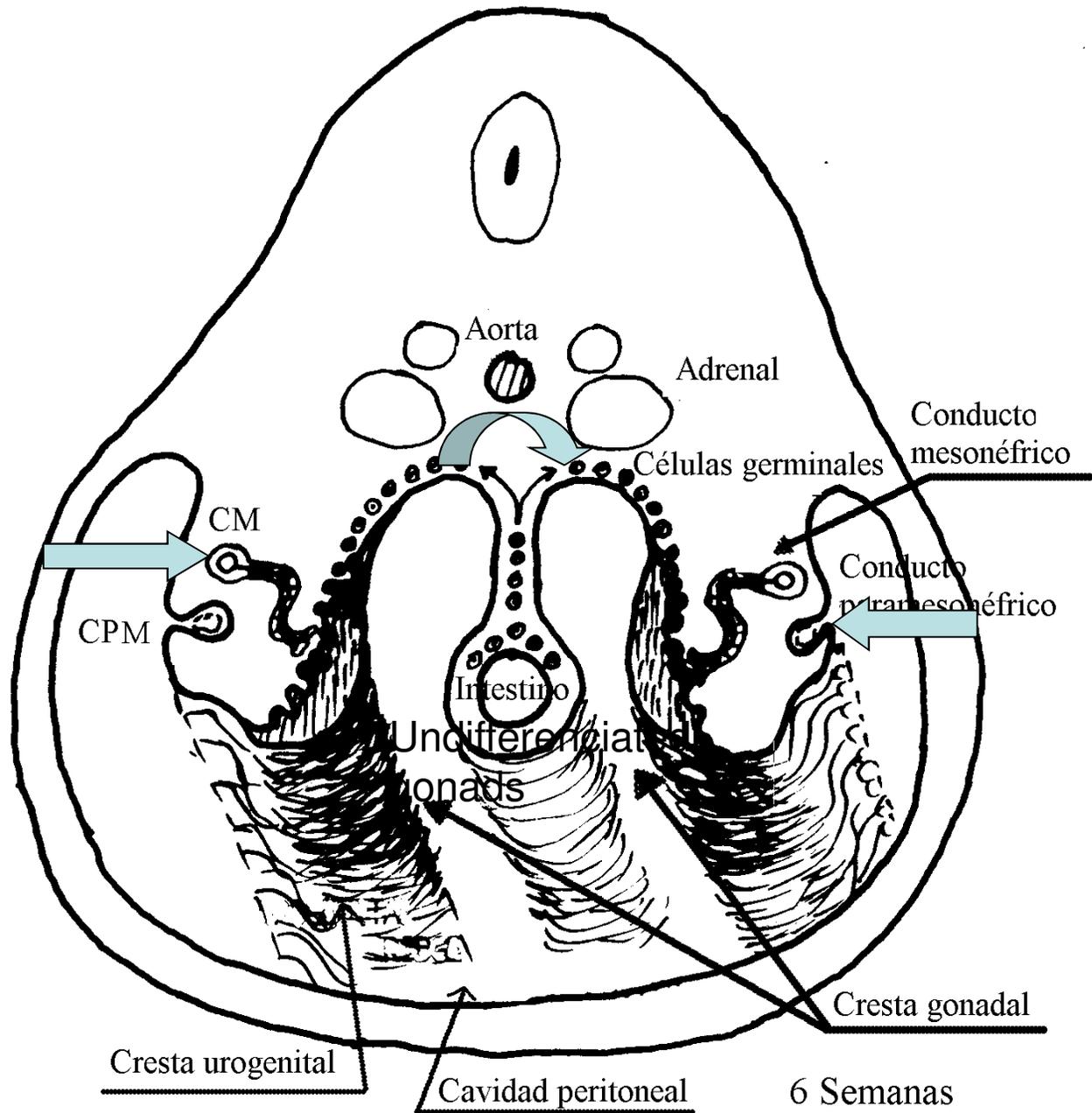
Embryological bases: GONADS

- Fifth week of pregnancy
- Wolff's body
- Urogenital ridge
- Somatic cells/ germ cells
- Teloferon. Fibronectin
- Primary sexual cords/ secondary

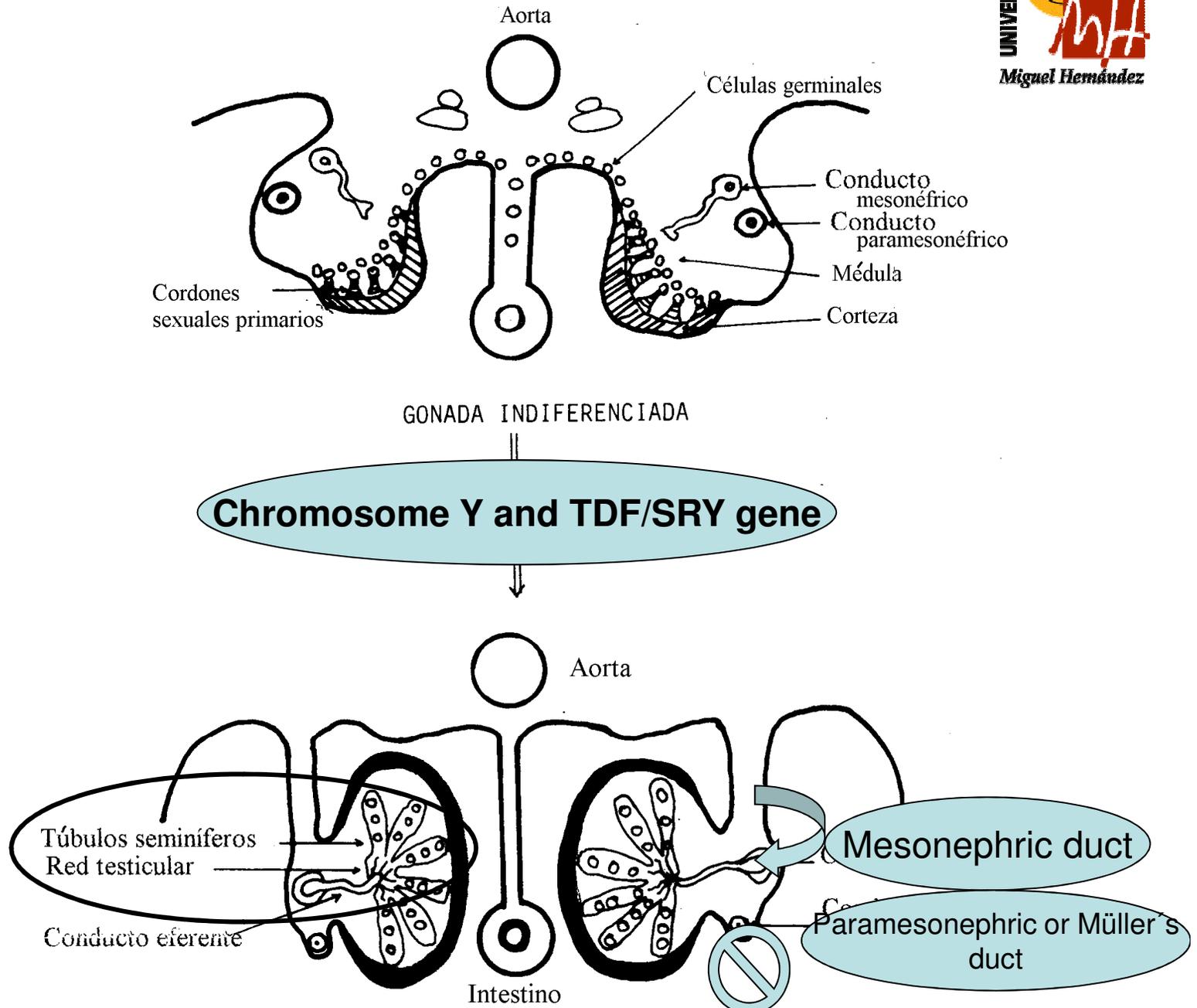


Moore and Persaud. The developing human. Fifth ed

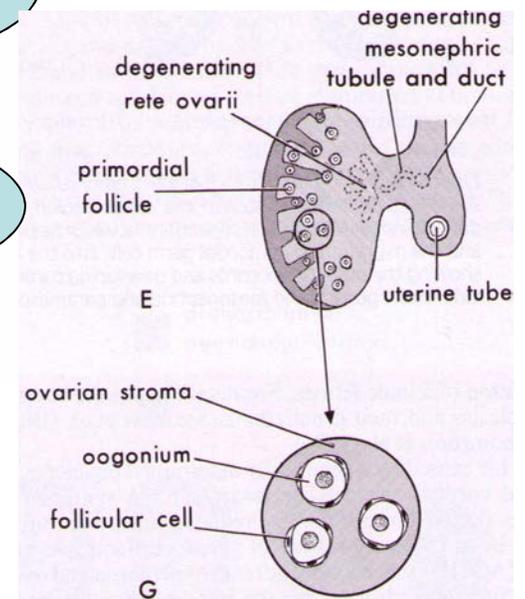
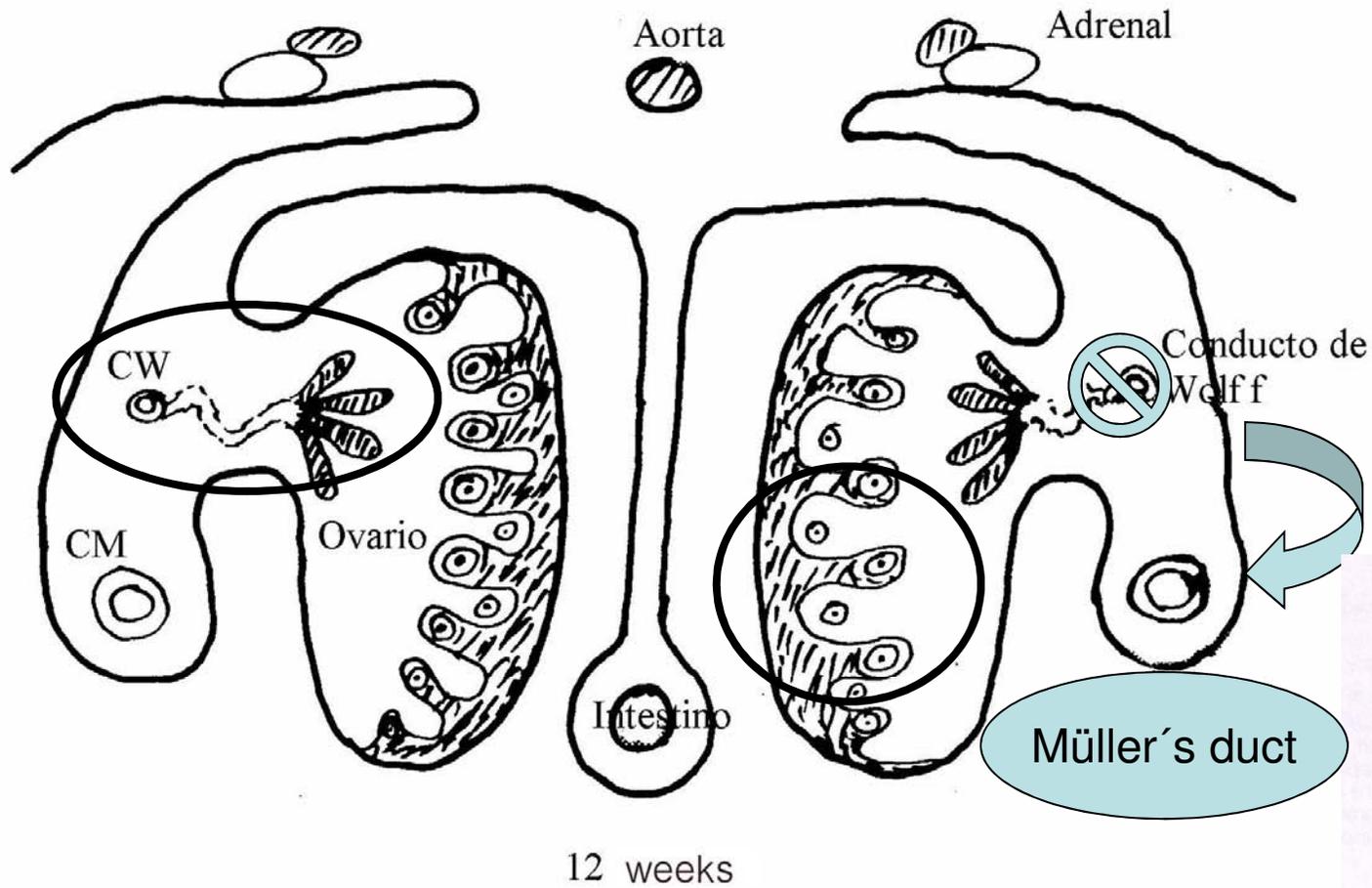
FORMATION AND DIFFERENTIATION OF THE GONADS



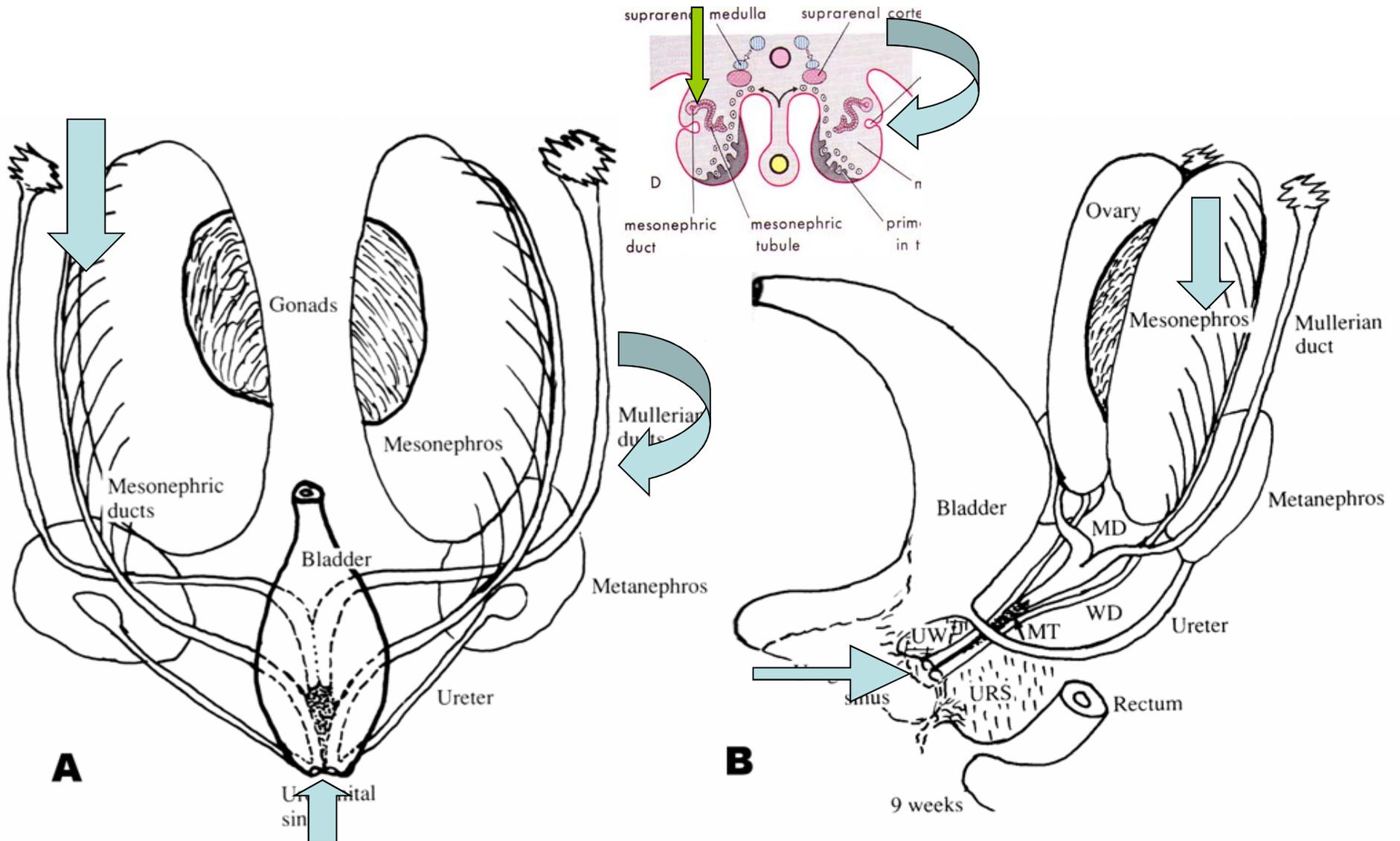
TESTIS DIFFERENTIATION

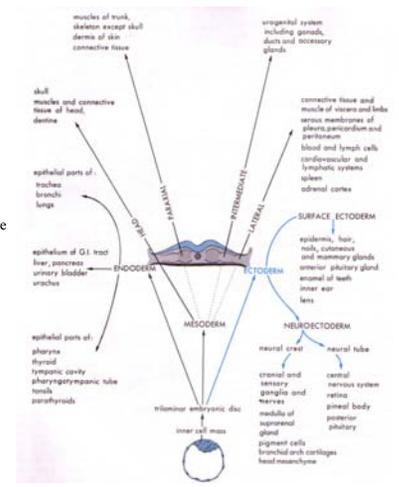
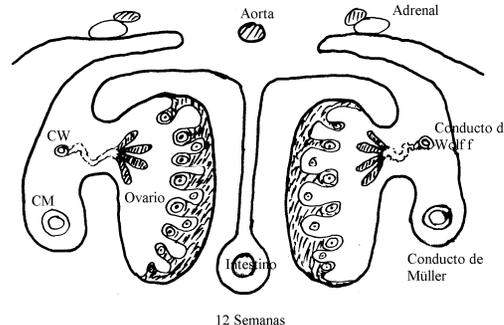
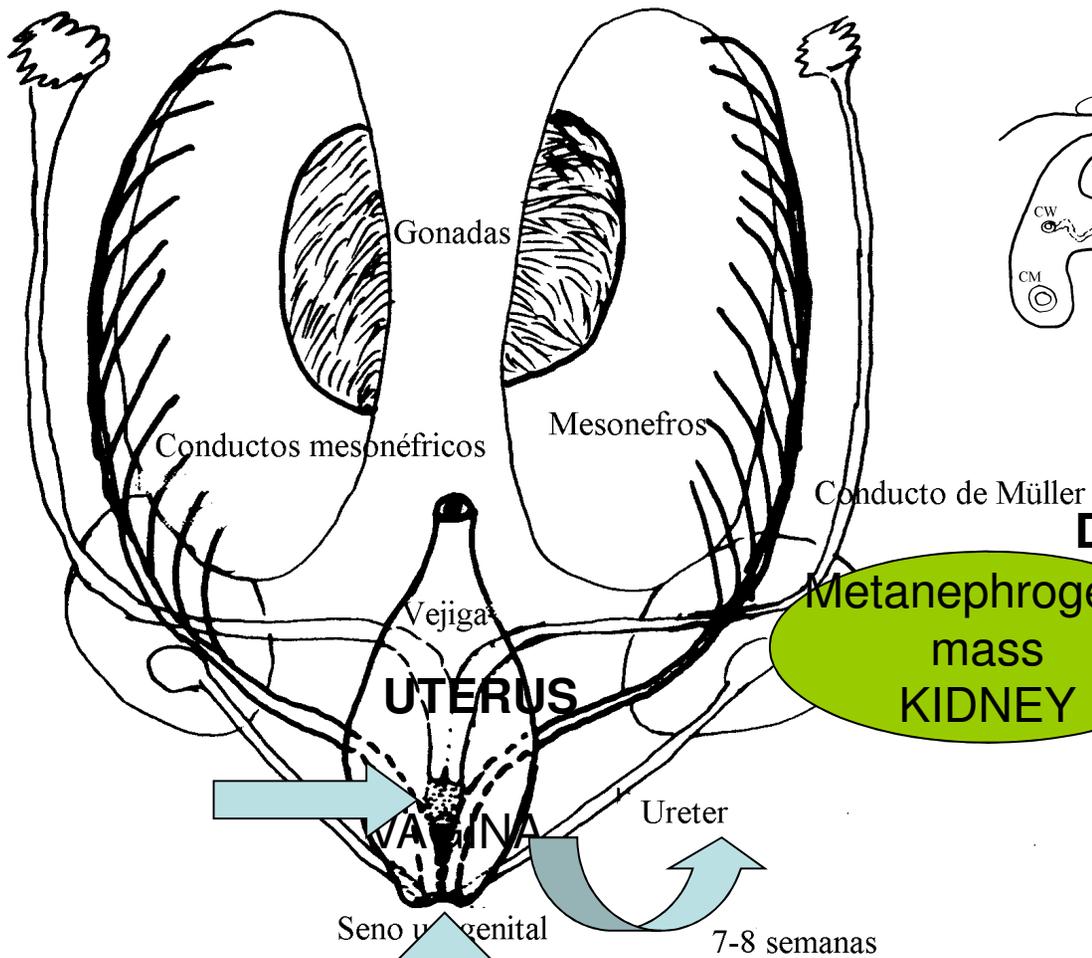


OVARIAN DIFFERENTIATION



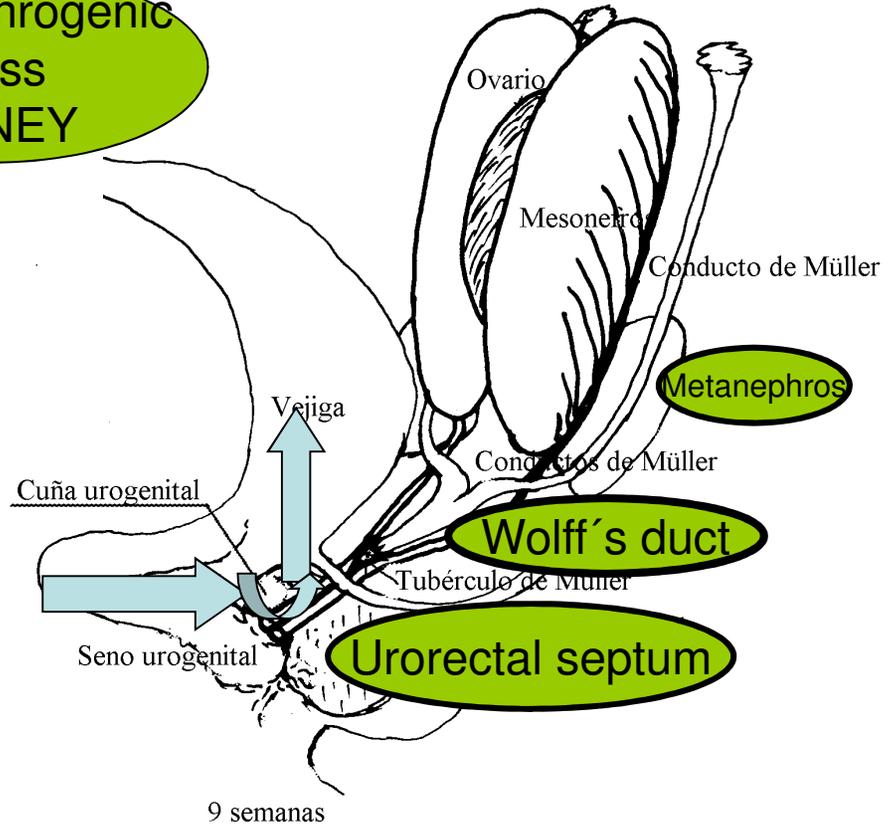
INTERNAL GENITALS AND URINARY SYSTEM





Development of the urinary system

Metanephrogenic mass KIDNEY

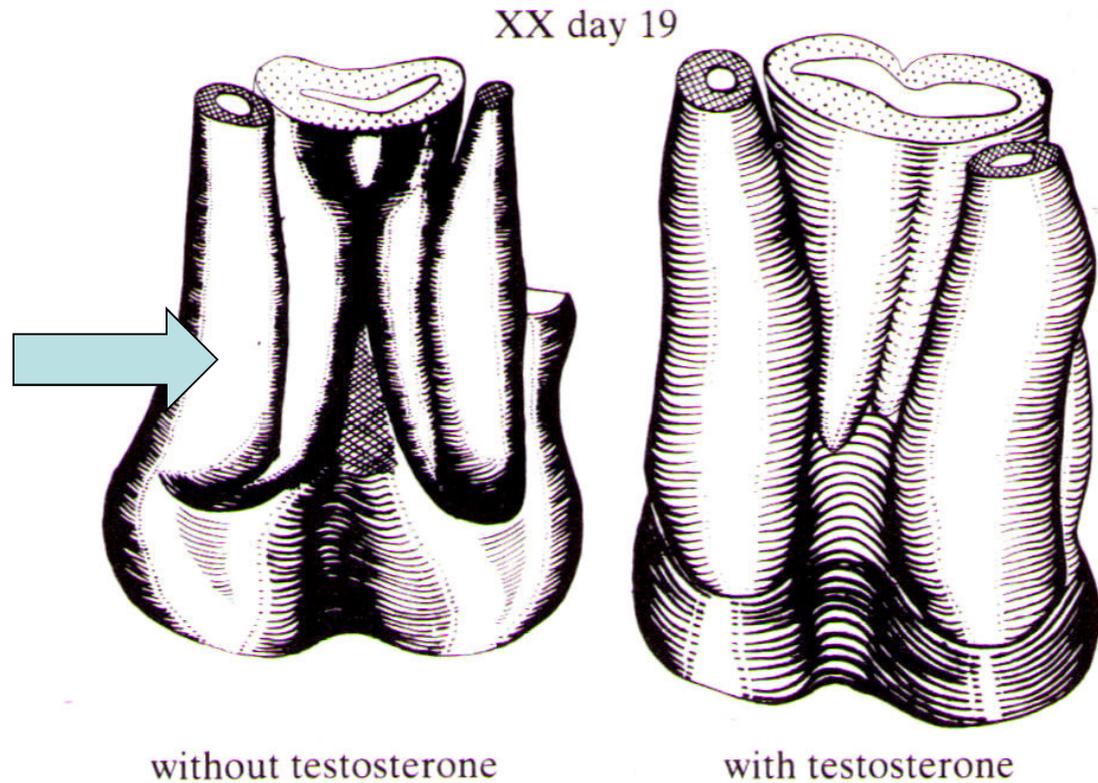
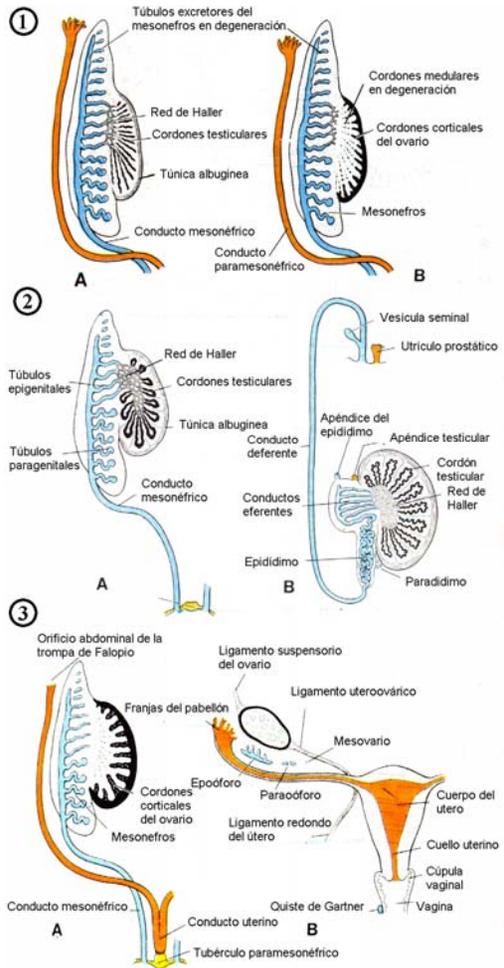


- Paramesonephric ducts
- Uterine primordium
- Müller tubercle
- Wolffian ducts
- Urogenital sinus
- Ureteral bud
- Inductor function of the mesonephric duct

9 semanas

Langman Embryology
(Sadler, 1986)

EMBRYOLOGY OF THE VAGINA



G. Bok and U. Drews,
J Embryol exp Morph 73, 275-95,
1983

Acién P. *Embryological observations on the female genital tract.* Hum Reprod 7;437-445, 1992

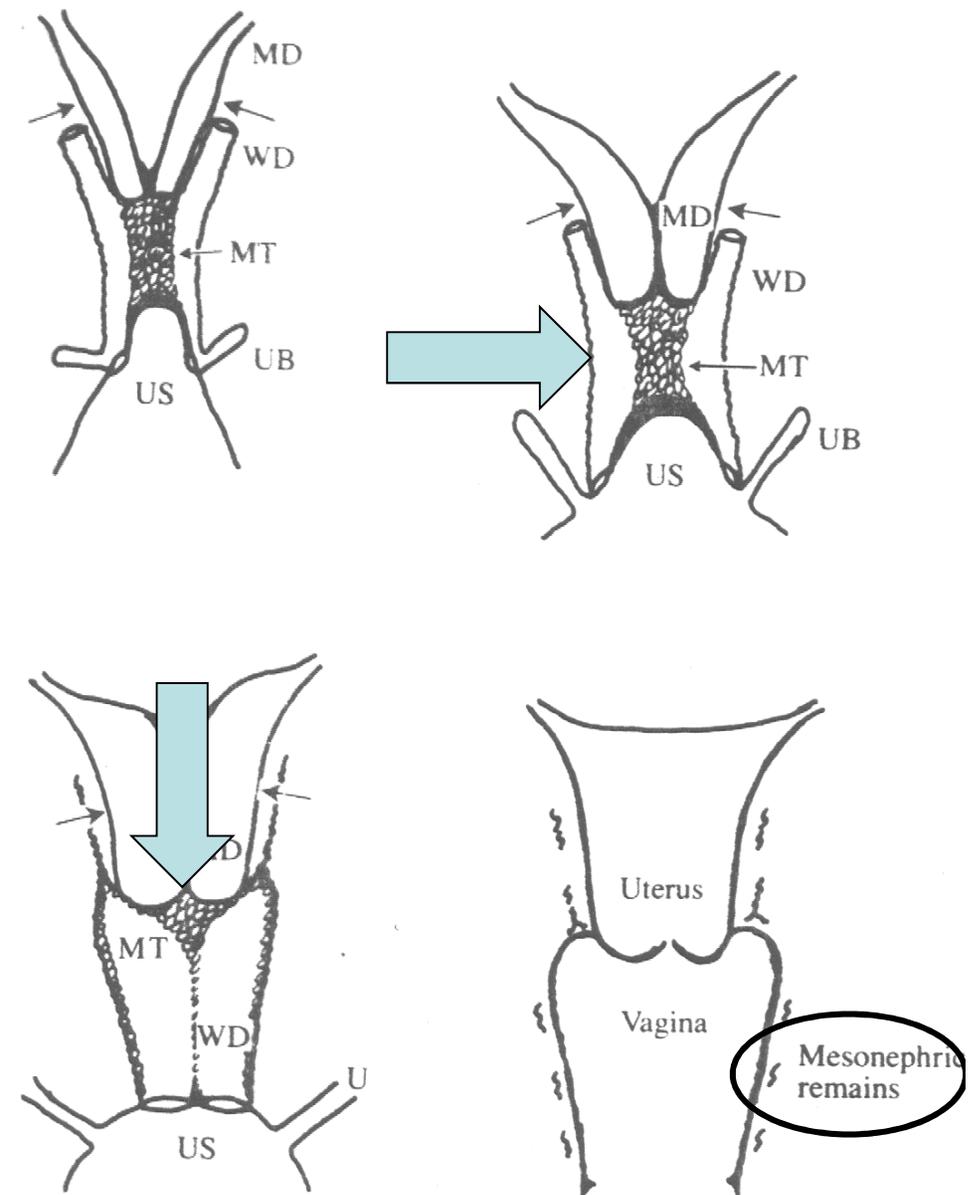
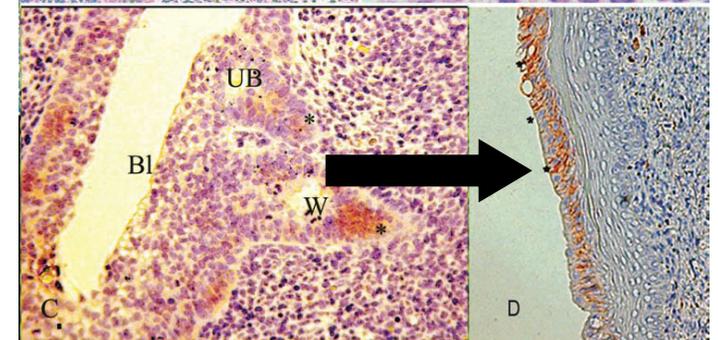
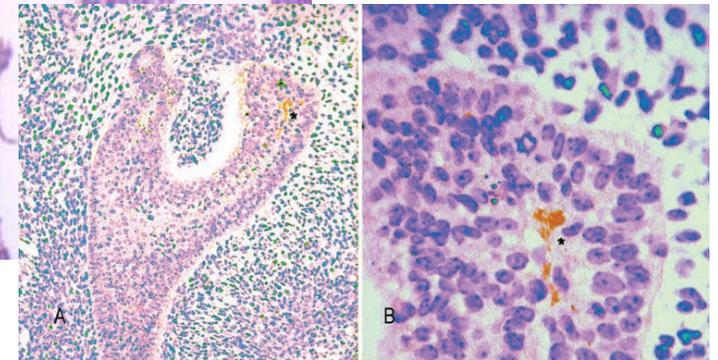
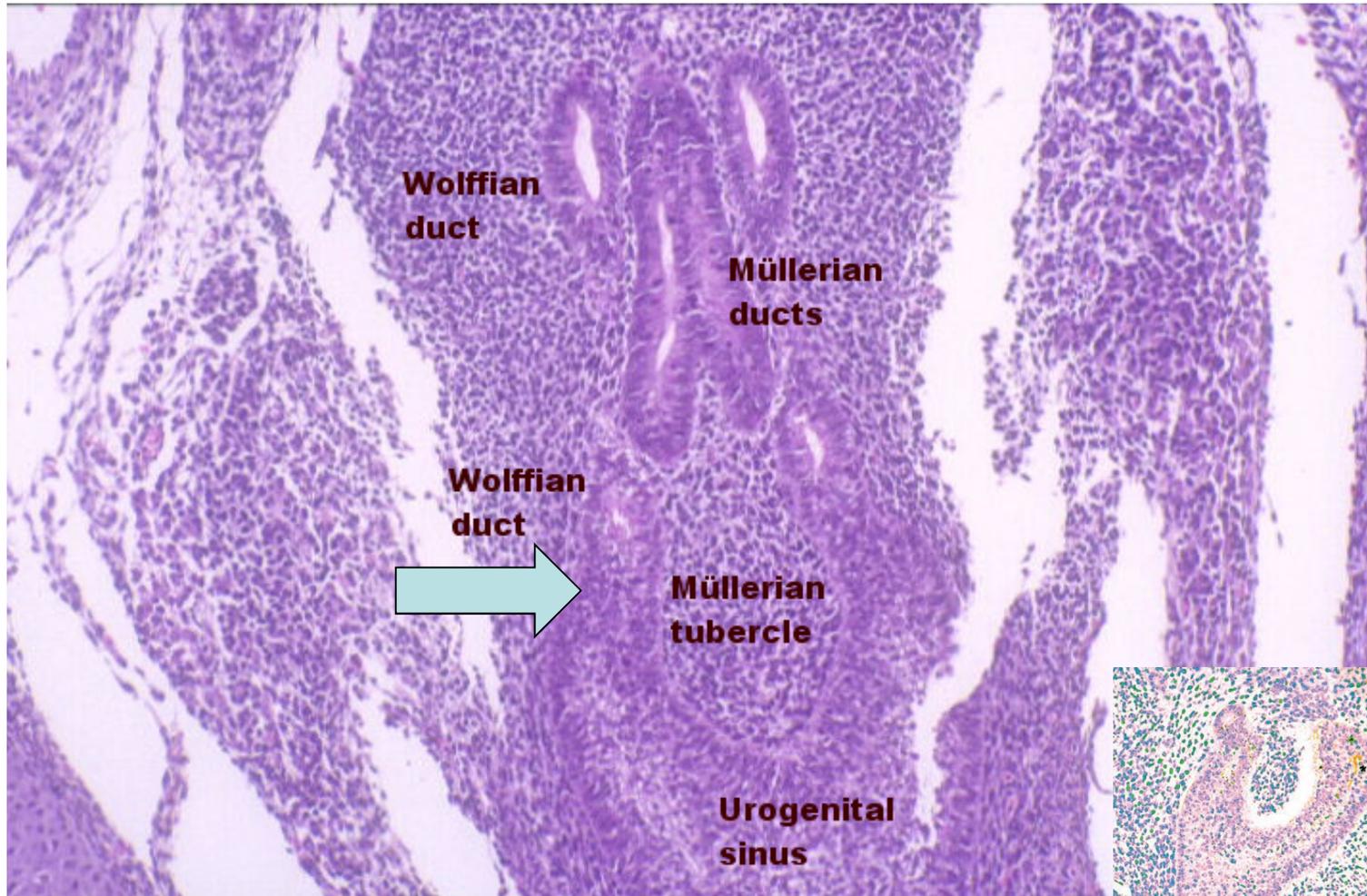
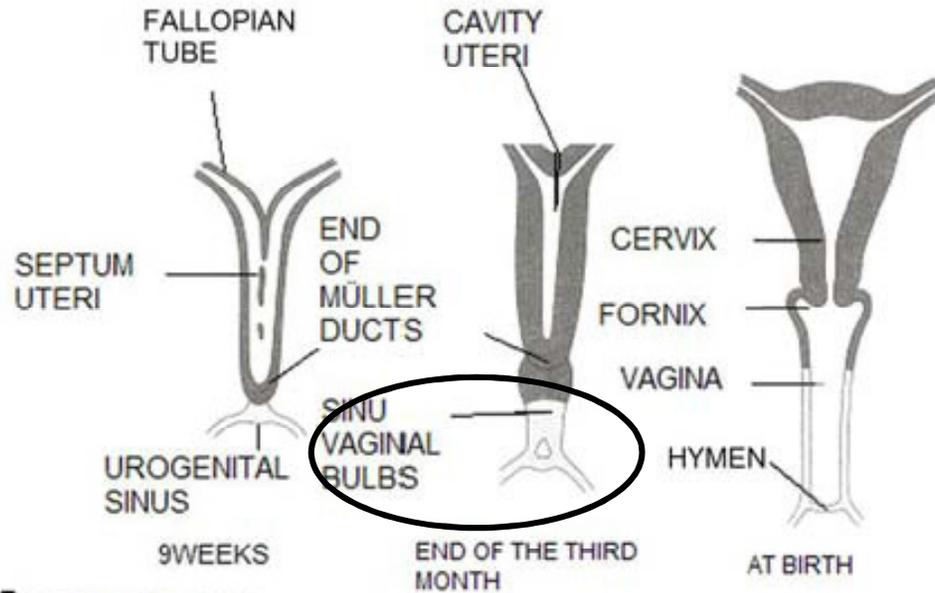


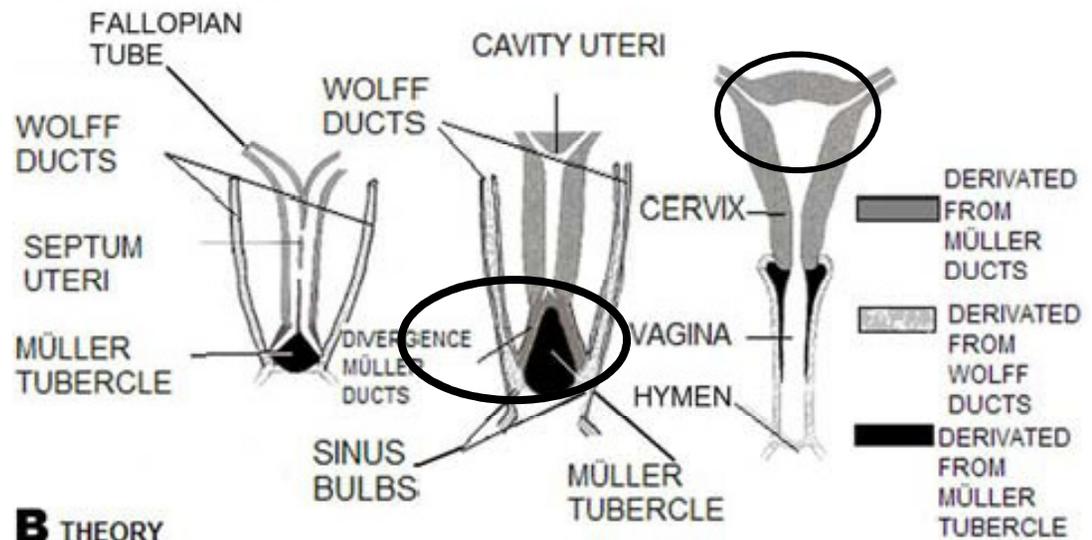
Fig. 9. Hypothesis of the embryological development of the human vagina. MD, paramesonephric or Müllerian duct; WD, mesonephric or Wolffian duct; MT, Müllerian tubercle; US, urogenital sinus; UB, ureteral bud; U, ureter.



Sanchez-Ferrer et al,
Hum Reprod 21;1623-28, 2006



A CLASSIC THEORY



B THEORY PROPOSED BY THE AUTHORS

Sanchez-Ferrer et al,
Hum Reprod 21;1623-28, 2006

Acién P. *Embryological observations on the female genital tract.* Hum Reprod 7;437-445, 1992

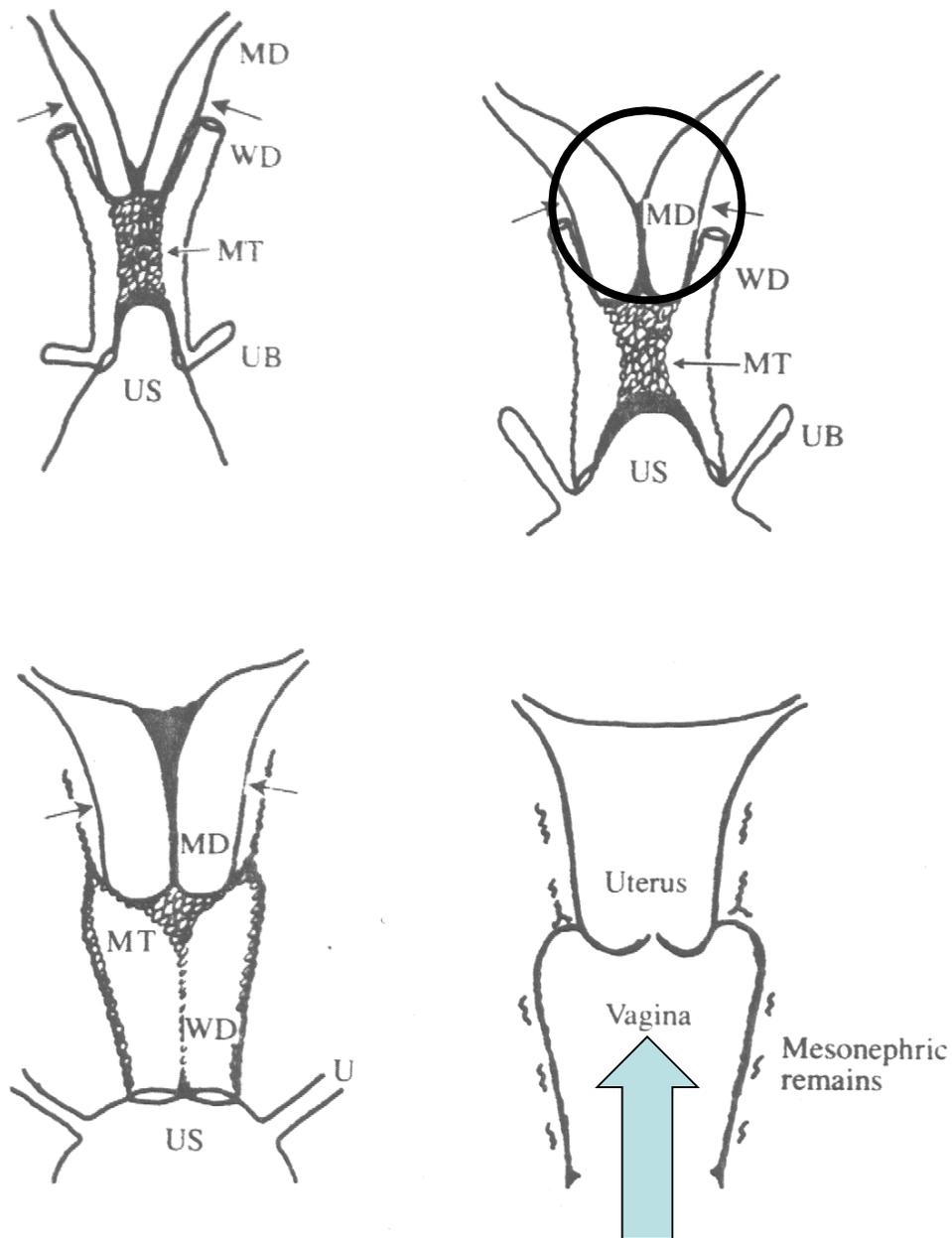
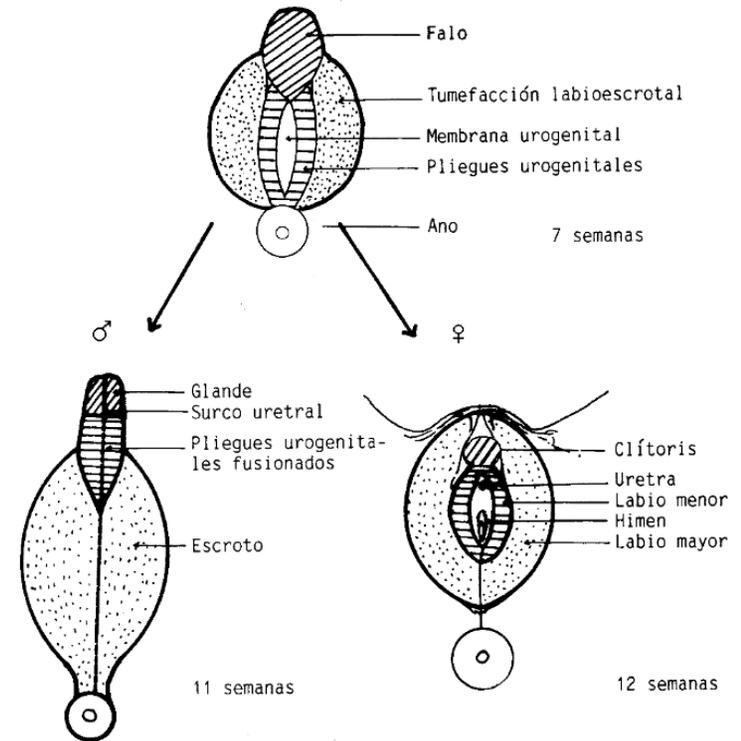
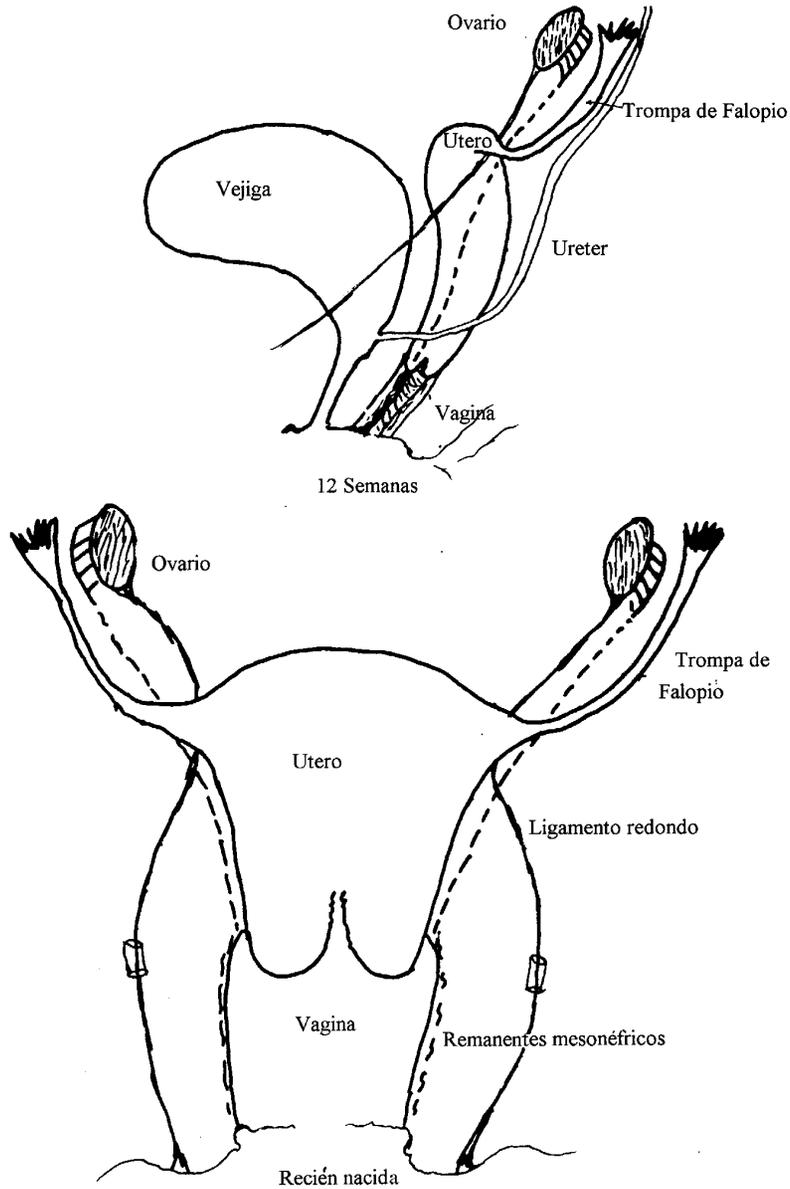
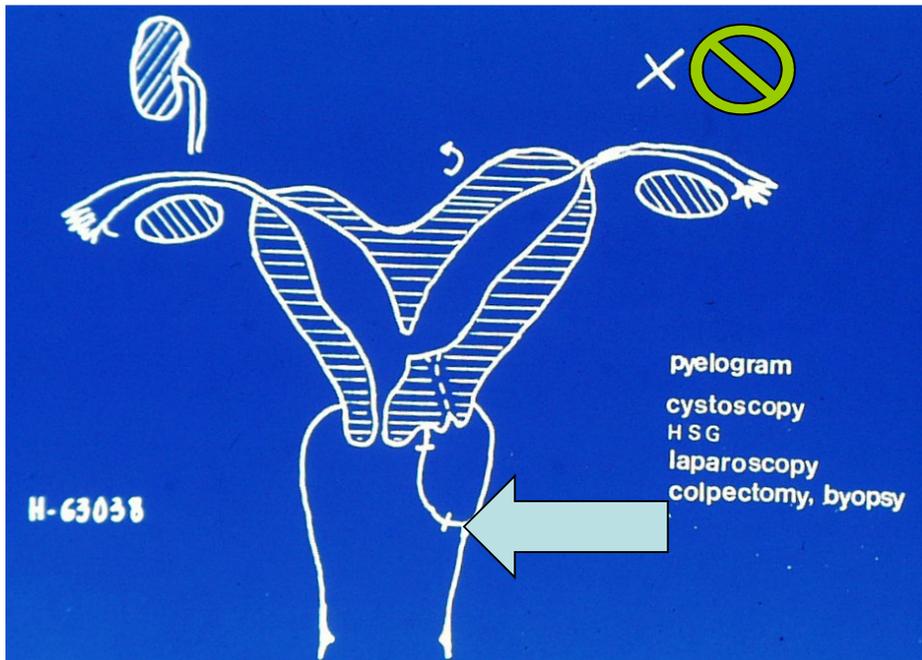
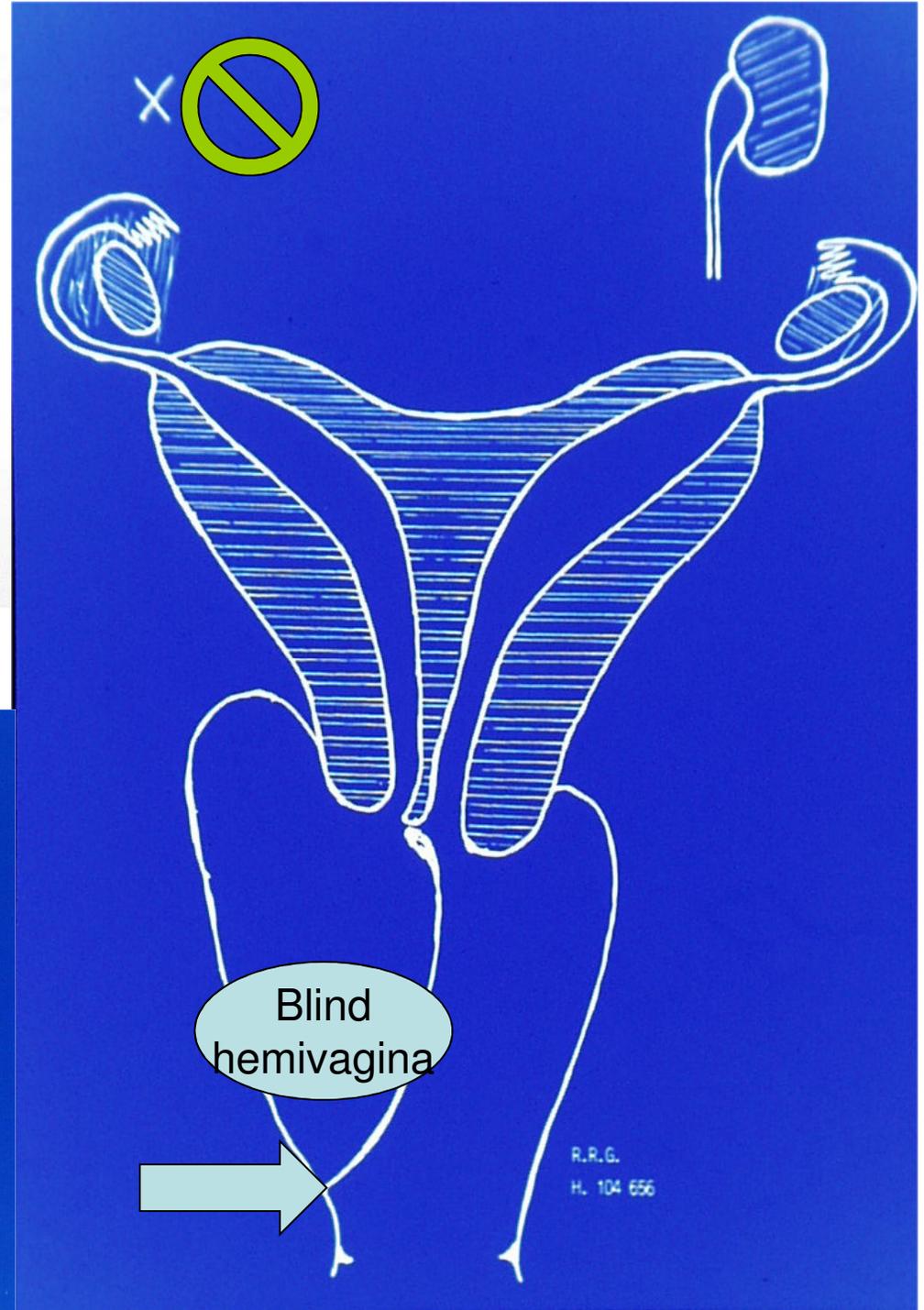
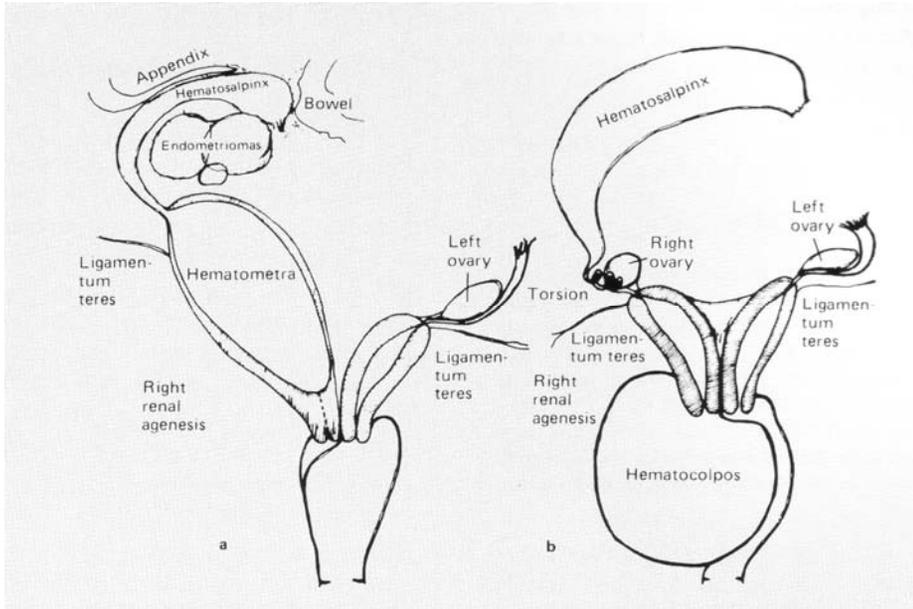


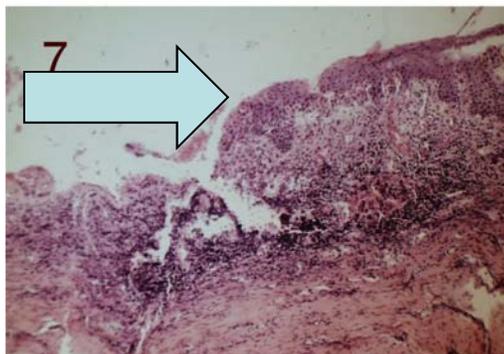
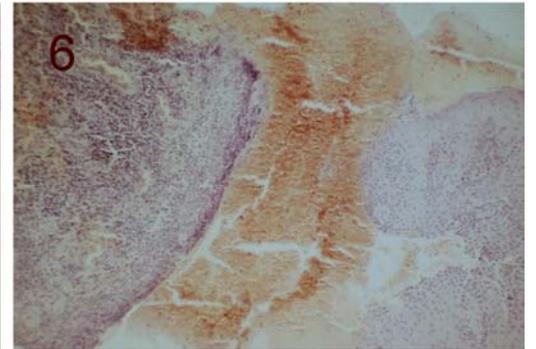
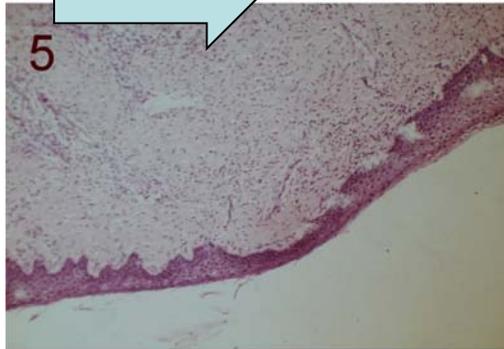
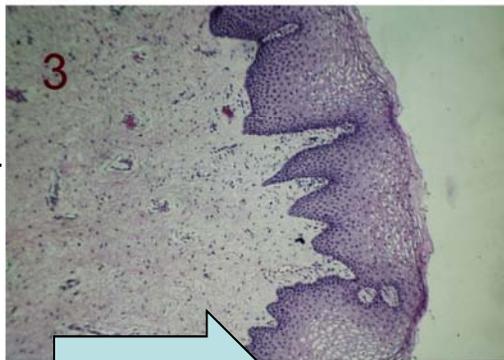
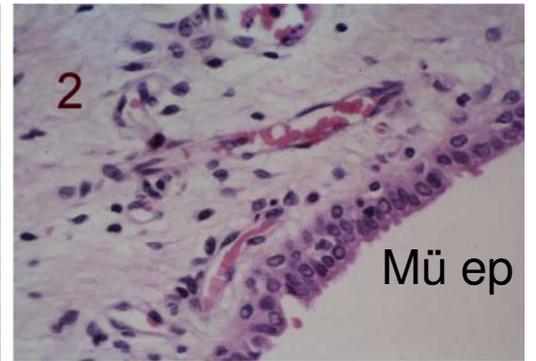
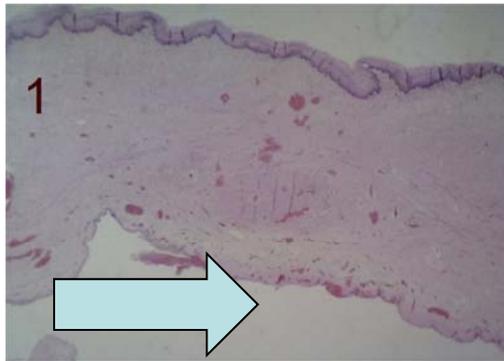
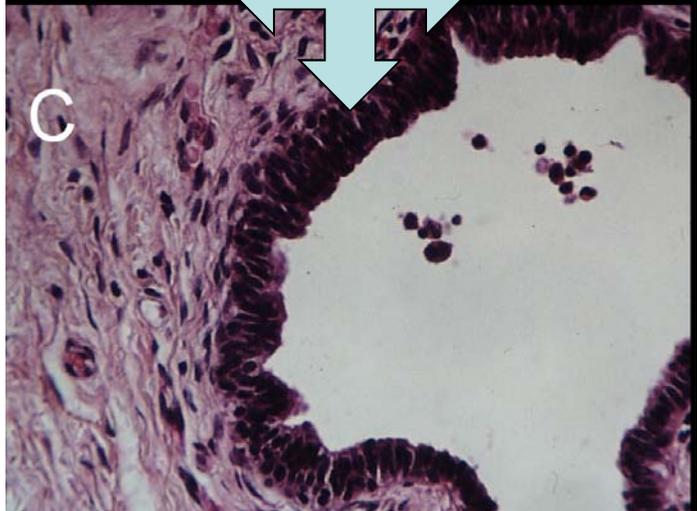
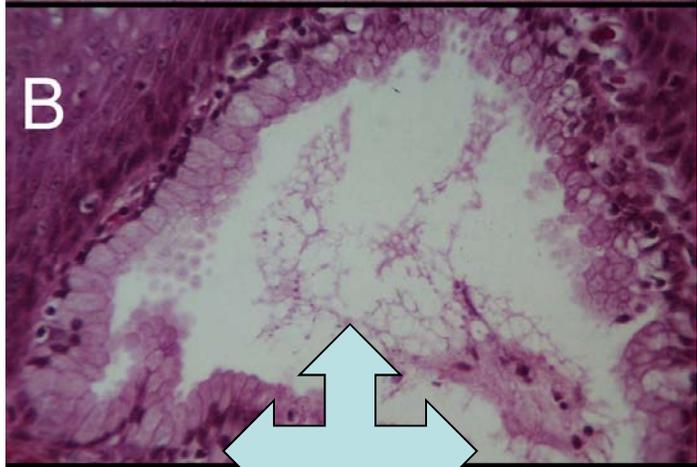
Fig. 9. Hypothesis of the embryological development of the human vagina. MD, paramesonephric or Müllerian duct; WD, mesonephric or Wolffian duct; MT, Müllerian tubercle; US, urogenital sinus; UB, ureteral bud; U, ureter.

Advanced development of the female genital tract

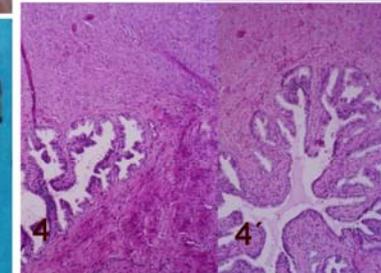
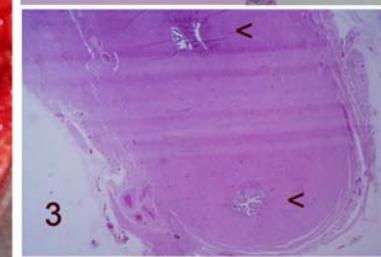
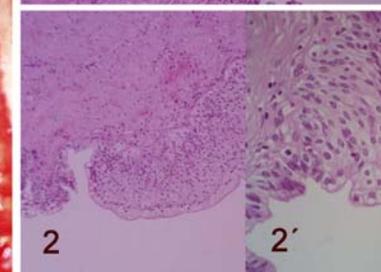
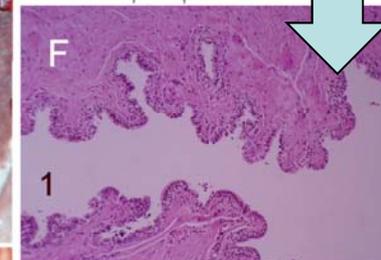
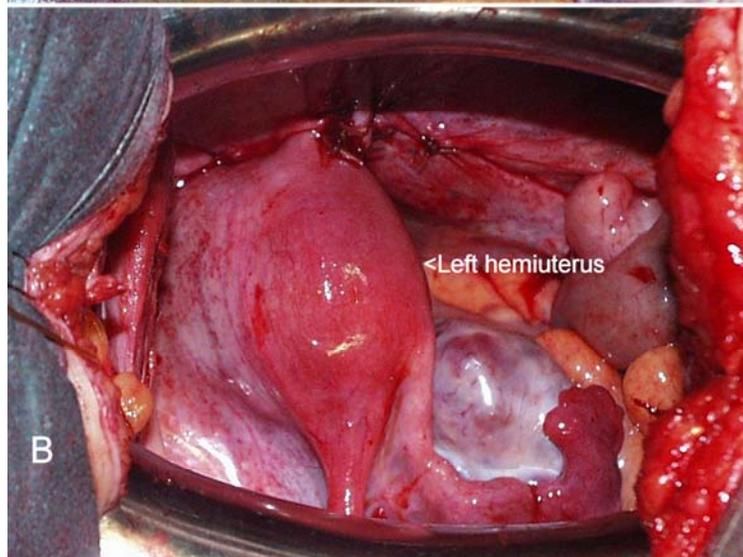
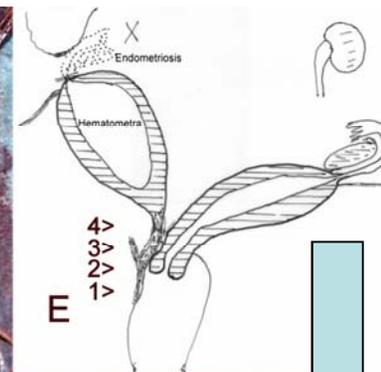
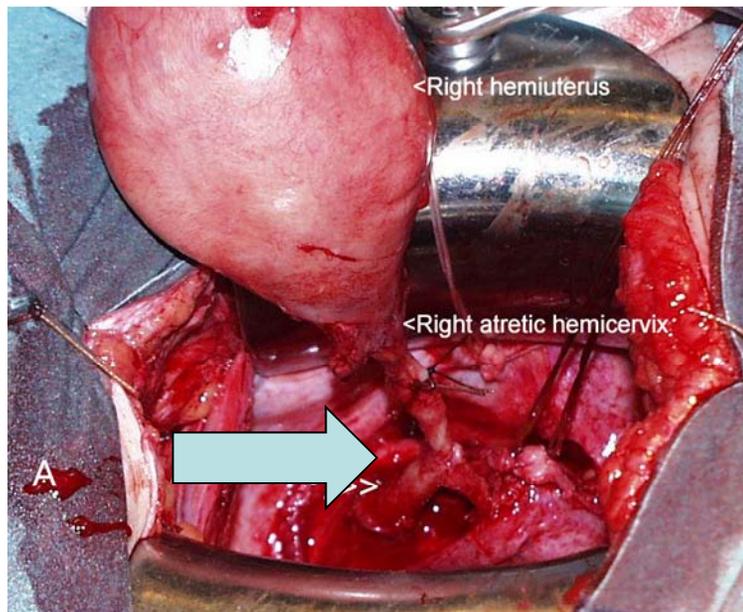
Differentiation of the external genitals







Acién et al,
 Eur J Obstet Gynecol
 Reprod Biol 117:249-251, 2004

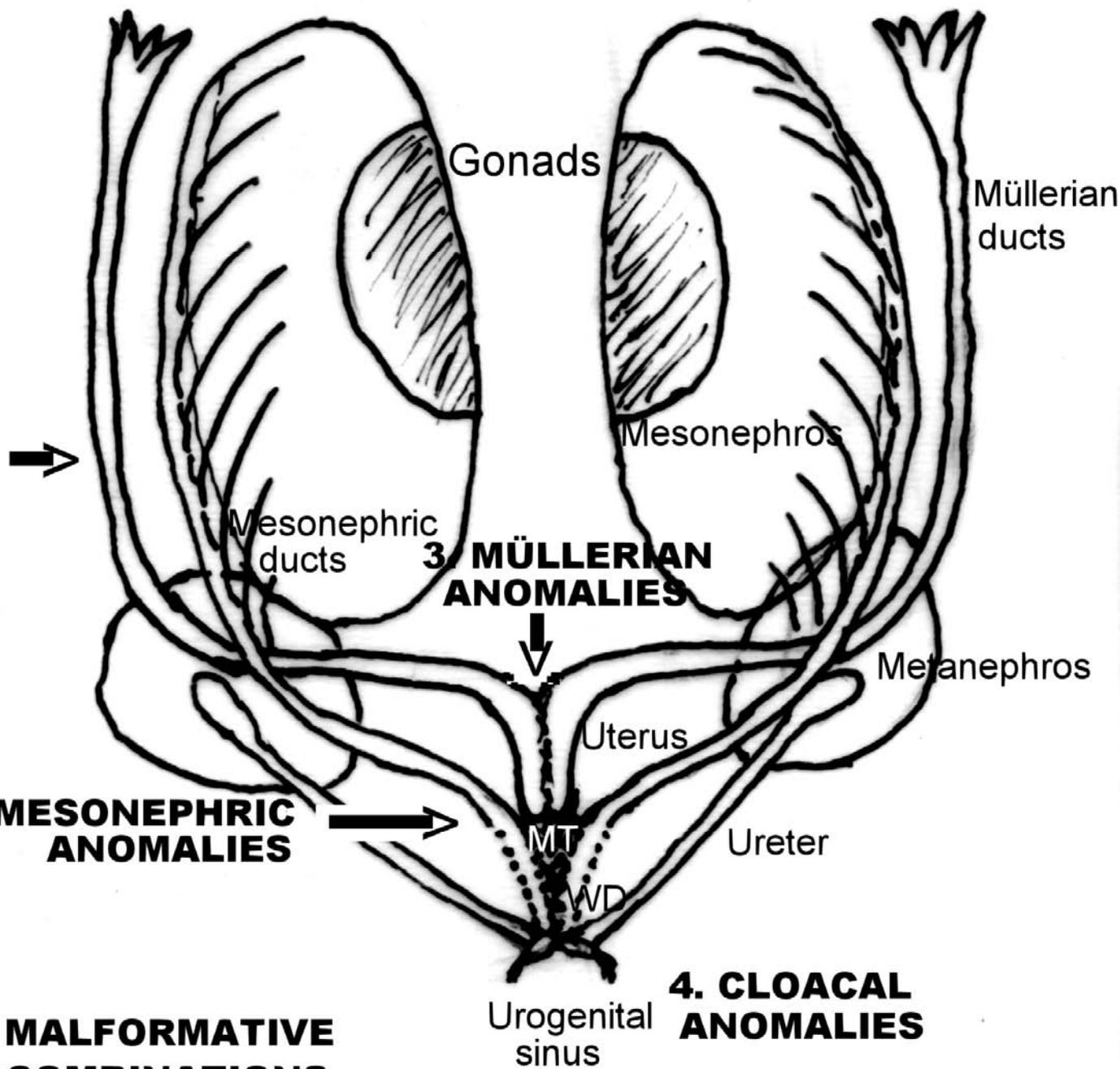


1. Cylindrical epithelium
2. Squamous metaplasia
3. Junction
4. Atretic cervix and possible mesonephric duct

In summary:

- 1. The appropriate development, fusion and reabsorption of the separating wall between both Müllerian ducts is induced by the Wolffian ducts placed at both sides and which act as guide elements
- 2. The fused Müllerian ducts form the uterus until the external cervical os. Mesonephric ducts enlarge caudally, form the sinuvaginal bulbs, incorporate the Müller tubercle's cells and give rise to the vaginal plate. By metaplastic induction or by epidermization from the sinus, the vagina is covered by a squamous epithelium
- 3. Since the ureteral bud sprouts from the opening in the Wolffian duct, the absence or distal injury of one of these ducts will give rise to a renal agenesis and blind or ipsilateral athretic hemivagina and uterine anomaly (fusion or reabsorption defect) due to a failure in the inducing function of the injured mesonephric duct.

**1. AGENESIS OF A WHOLE
UROGENITAL RIDGE**



Clinical-embryological classification of the female genital malformations

1. **Ageneis or hypoplasia** of a whole *urogenital ridge*

2. **Mesonephric anomalies**, with absence of the Wolffian duct opening to the urogenital sinus and of the sprouting ureteral bud.

- a) With large hematocolpos in the blind vagina.
- b) With Gartner's pseudocyst in the anterolateral wall of the permeable vagina.
- c) With partial reabsorption of the intervaginal septum.
- d) With complete unilateral vaginal or cervico-vaginal agenesis.

3. **Isolated müllerian anomalies**, can affect:

a) **Müllerian ducts**: uterine and or tubal anomalies, sometimes segmentary (*UTERINE ANOMALIES, ASRM classification*). *Other Müllerian anomalies*

b) **Müllerian tubercle**: vaginal (or cervico-vaginal) agenesis or atresia, and segmentary atresias as the transverse vaginal septum.

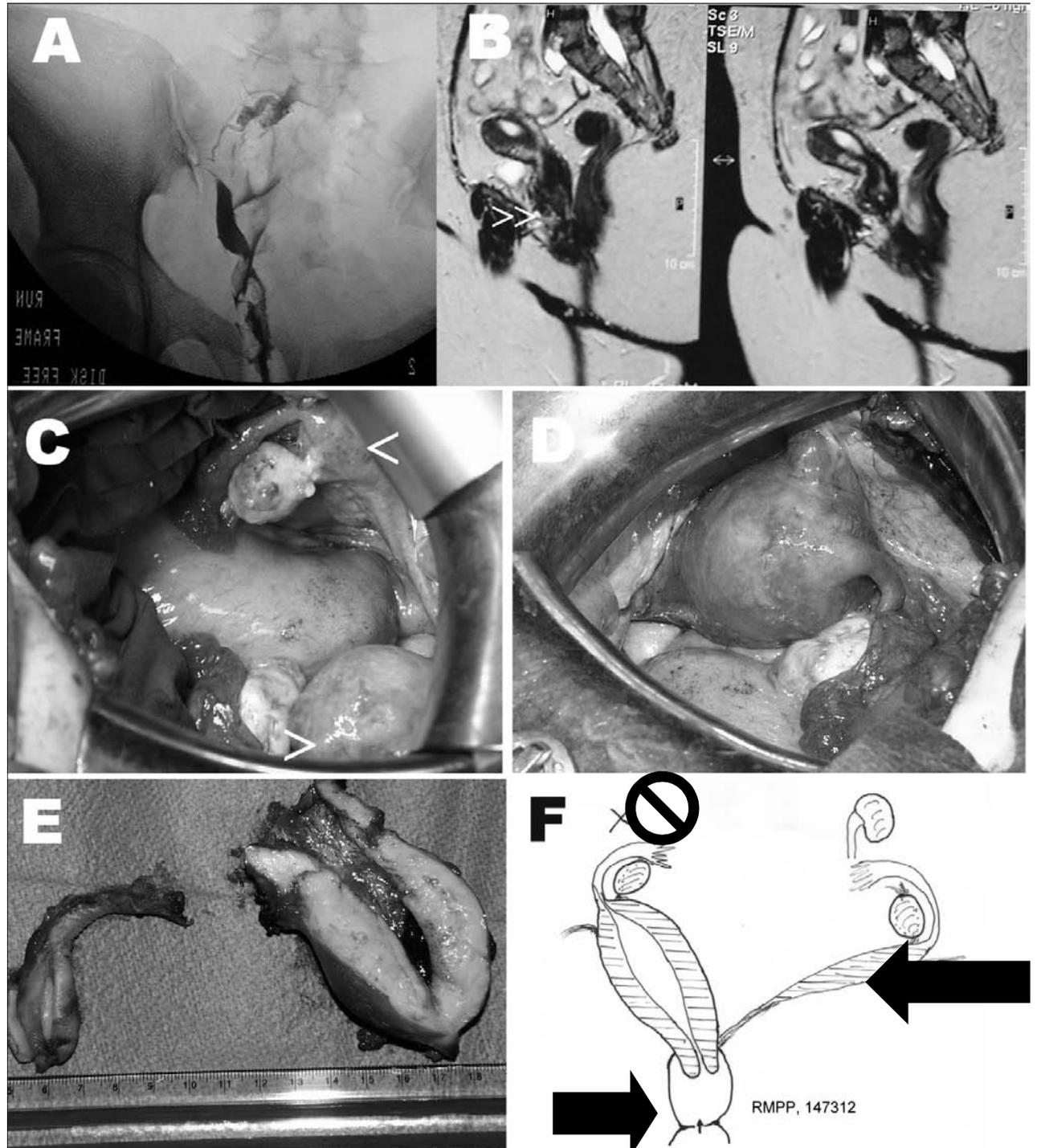
c) **Both** Müllerian tubercle and ducts (Rokitansky syndrome, uni or bilateral)

4. Anomalies of the **urogenital sinus** (hymen, cloacal anomalies)

5. **Malformative combinations**

Malformative combinations

Acién et al,
Hum Reprod 19:2377-84,
2004



Clinical-embryological classification of the female genital malformations

4. Isolated Müllerian anomalies:

a) Müllerian ducts:

Uterine and or tubal anomalies, sometimes segmentary

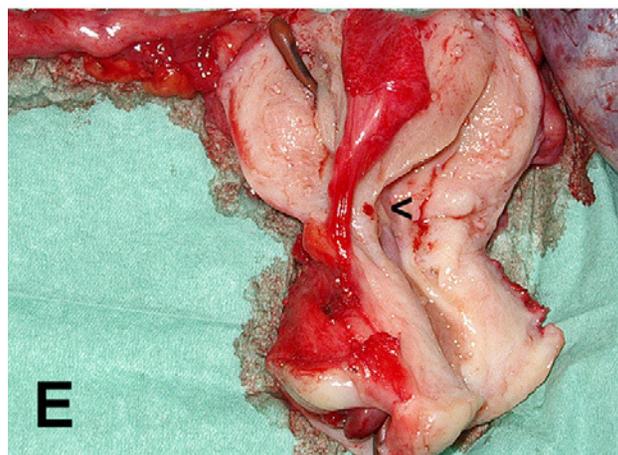
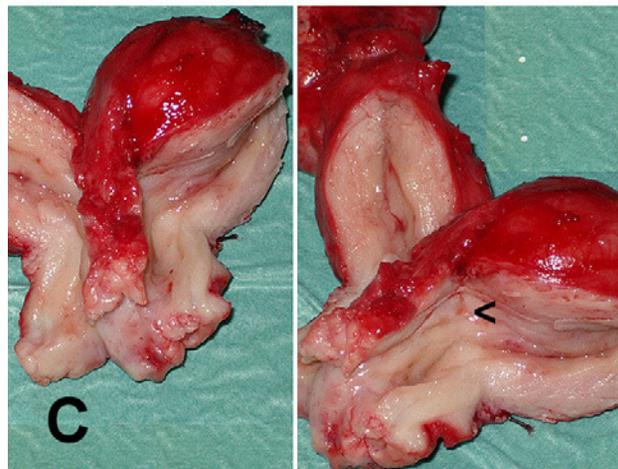
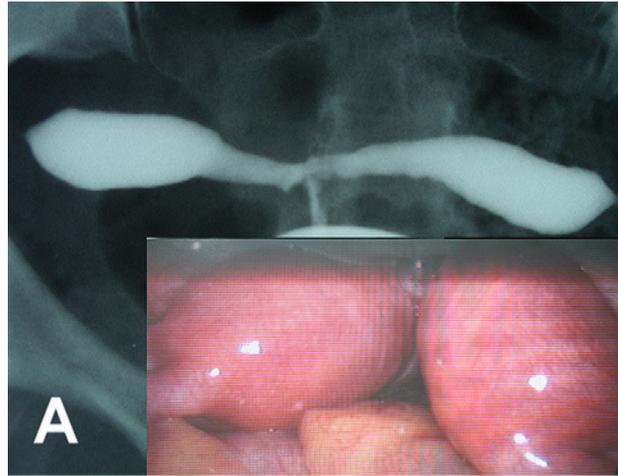
(UTERINE ANOMALIES, ASRM classification).
Other Müllerian anomalies

Other Müllerian anomalies:

- Müllerian anomalies “without a classification”: from the didelphys-unicollis uterus to the bicervical uterus with or without septate vagina (Fertil Steril [2008, march 24, epub] 2009; 91:2369-75):
discrepancy in the fusion and resorption processes between both uterine segments (superior and inferior) corresponding to the converging and diverging portions of the Müllerian ducts.
- **Segmentary defects.**
Segmentary atresias in Müllerian malformations (Eur J Obstet Gynecol Reprod Biol 2008; 141:188-9)
- **Affectation or absence of affectation of the Müllerian tubercle**

Acién et al
Fertil Steril 2009;91:2369-75

Classifying Müllerian anomalies



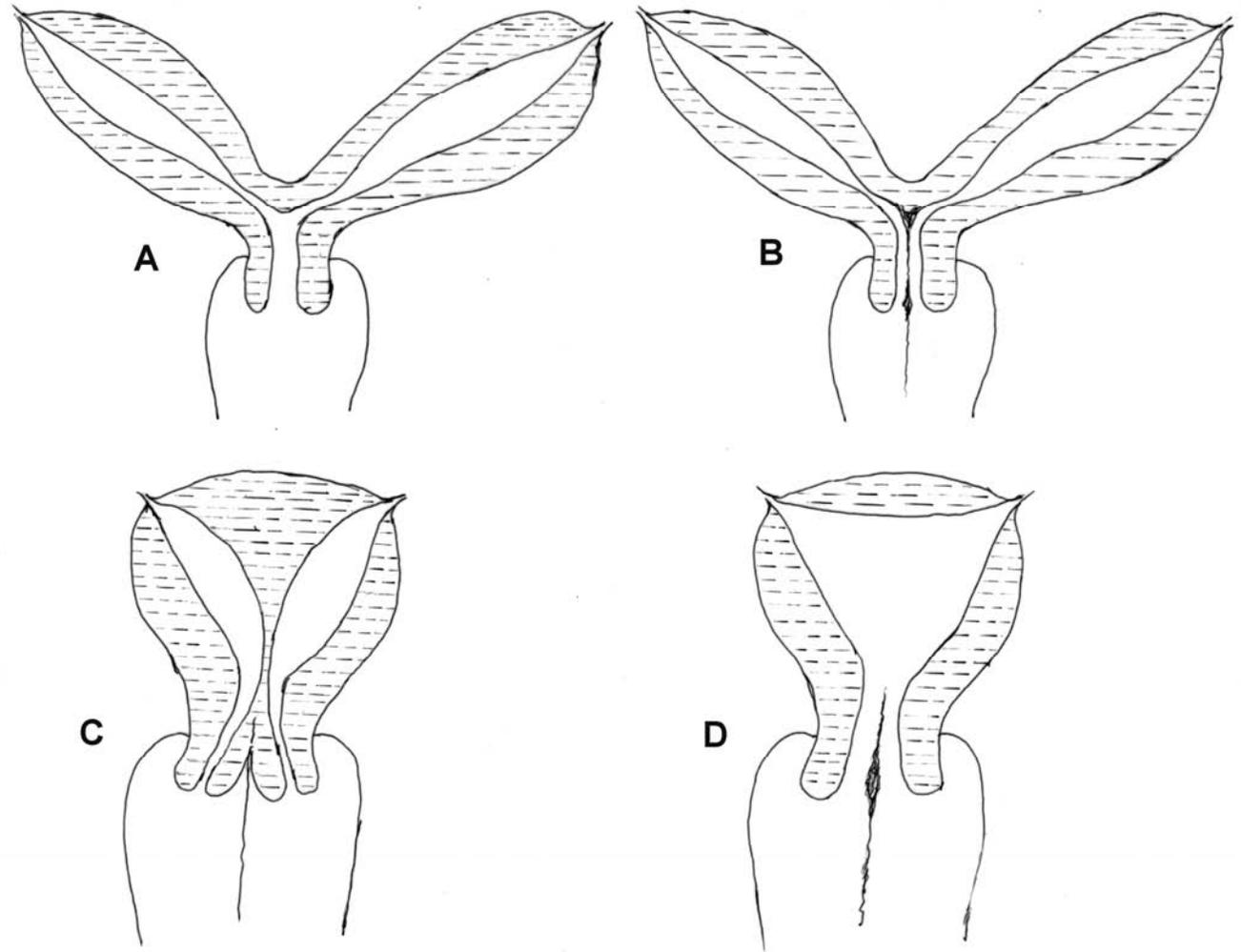
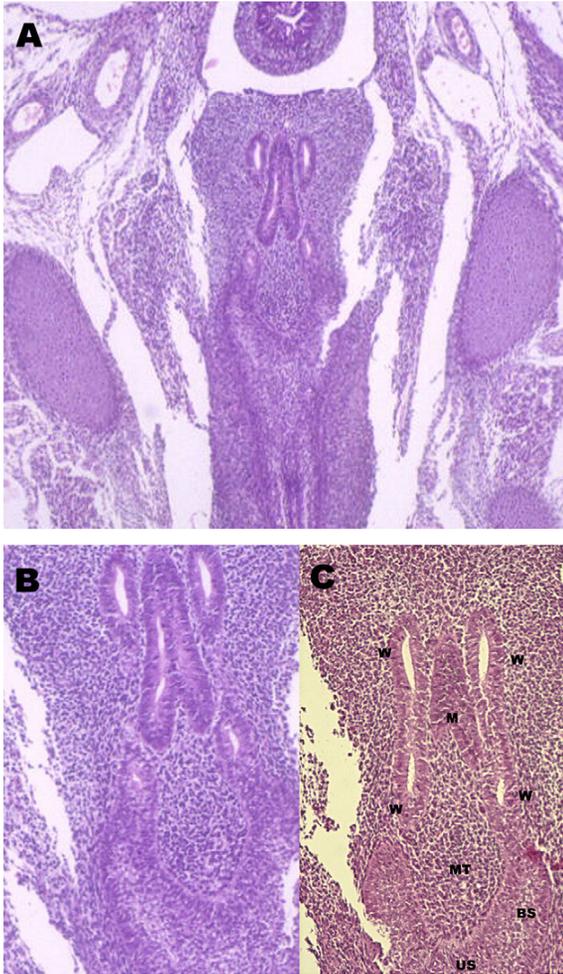
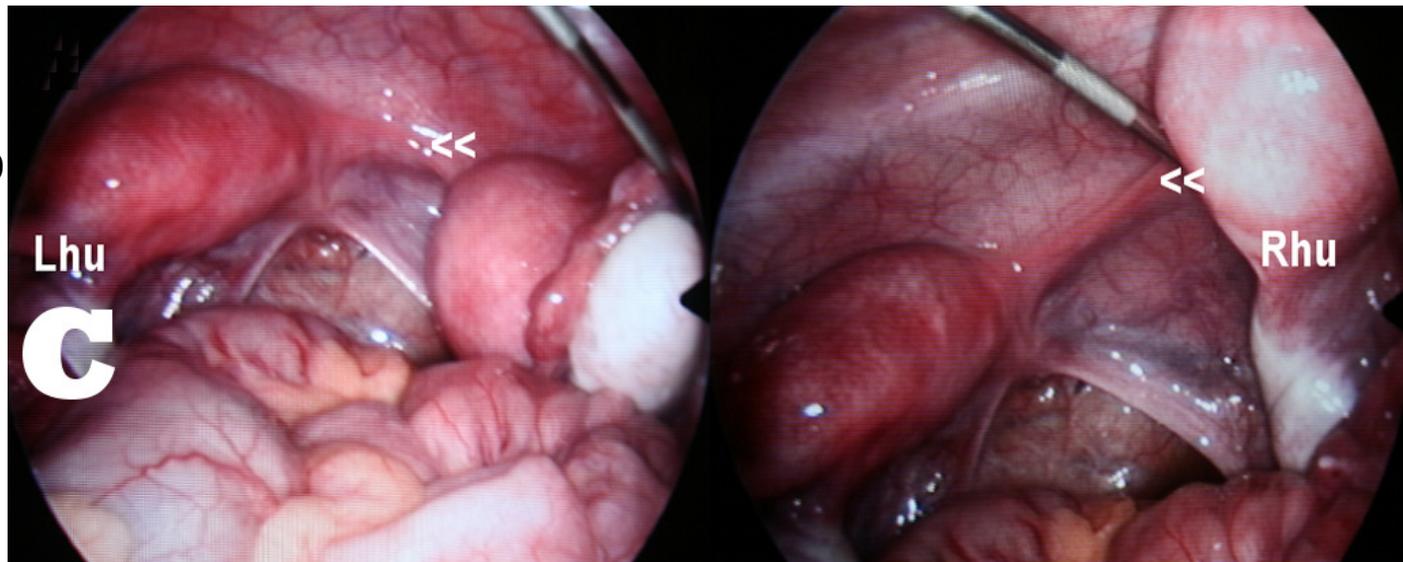


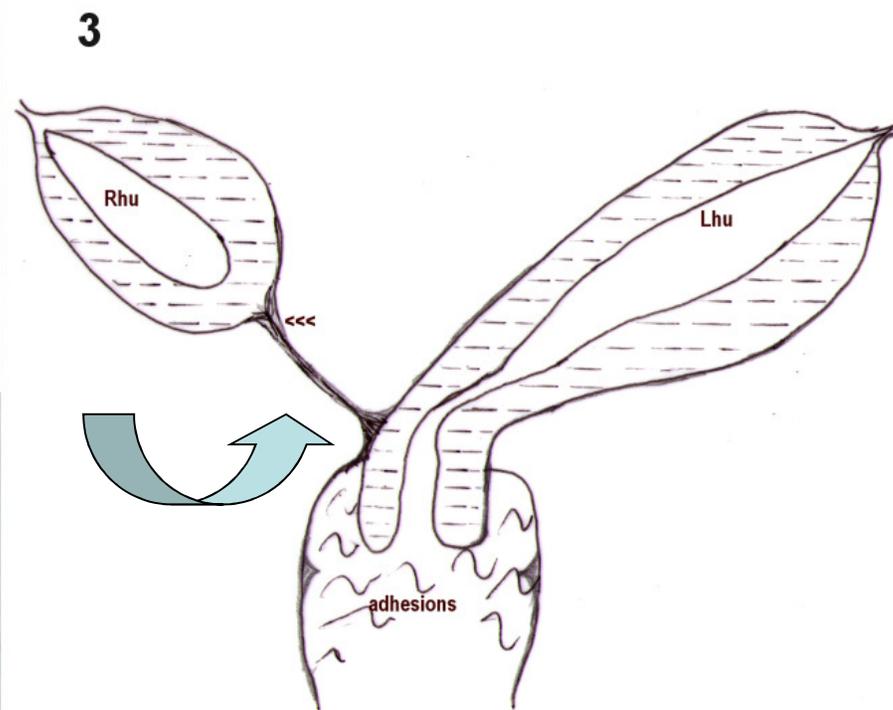
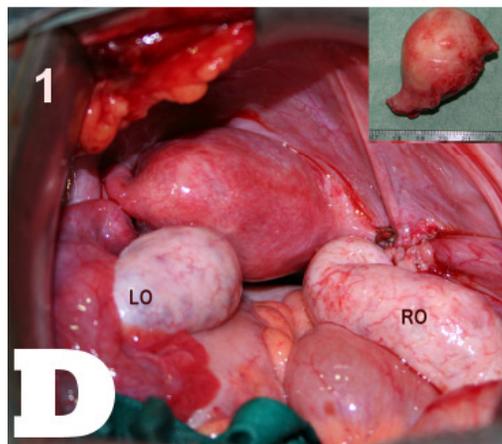
Diagram of fusion and/or resorption defects independent in the superior and inferior uterine segments:

- (A) Fusion defect of the superior uterine segment without defects in the cervix or vagina;
- (B) Fusion defect in the superior uterine segment and a resorption defect in the inferior segment and vagina;
- (C) Resorption defect in the superior uterine segment and a fusion defect in the inferior uterine segment, generally with septate vagina;
- (D) Resorption defects in the inferior uterine segment (cervix) and in the vagina, with normal development of the uterus (superior uterine segment).

Acién et al
Eur J Obstet Gynecol
Reprod Biol 2008;141:188-9



Segmentary
atresias in
Müllerian
malformations



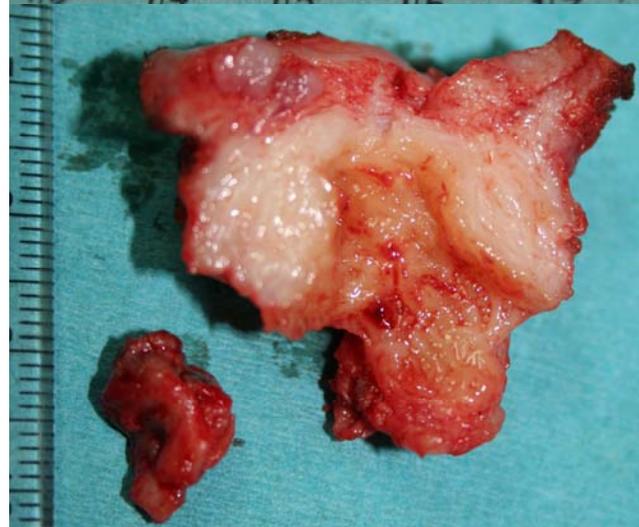
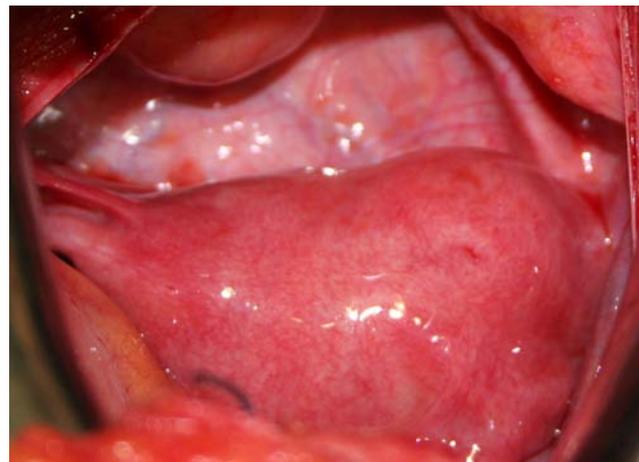
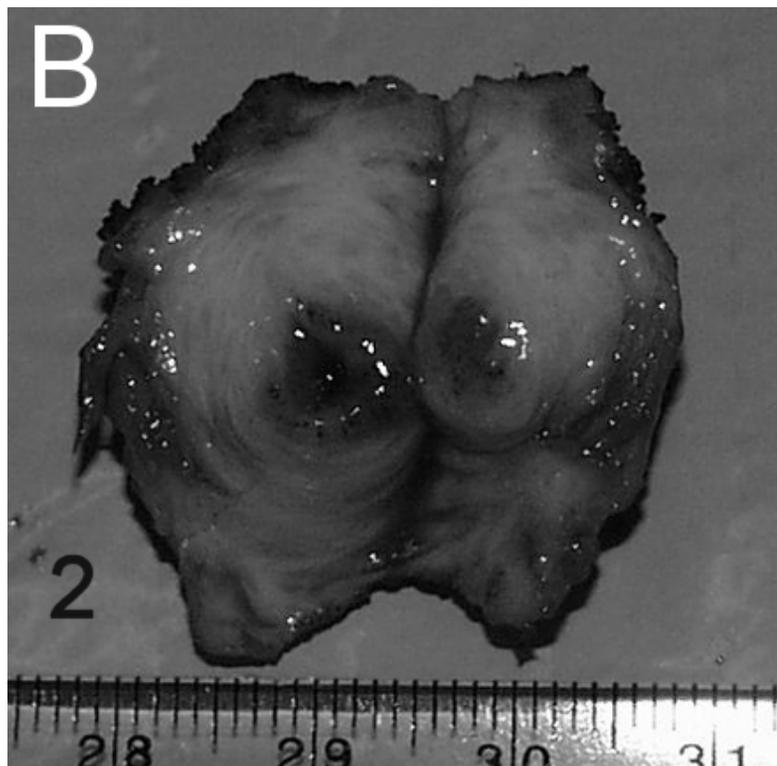
OTHERS ANOMALIES FROM:

Mesonephric remnants

GARTNER CYSTS

Müllerian remnants

ACCESORY UTERINE HORNS or APPENDICES





**THANK YOU VERY MUCH
FOR YOUR ATTENTION!**

