



THE ROLE OF GUBERNACULUM IN TESTICULAR MIGRATION – TRANSLATIONAL ASPECTS APPLIED TO UNDESCENDED TESTIS

Luciano A. Favorito MD, PhD

Full Professor – Urogenital Research Unit – State University From Rio de Janeiro
EDITOR In CHIEF - INT BRAZ J UROL



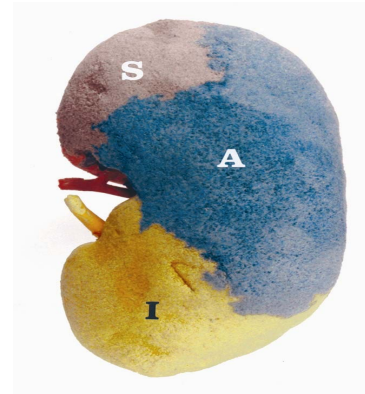
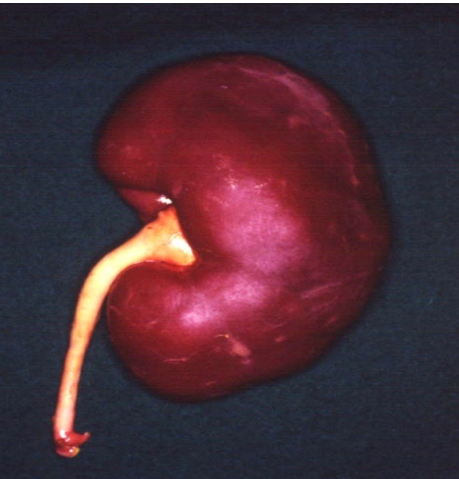
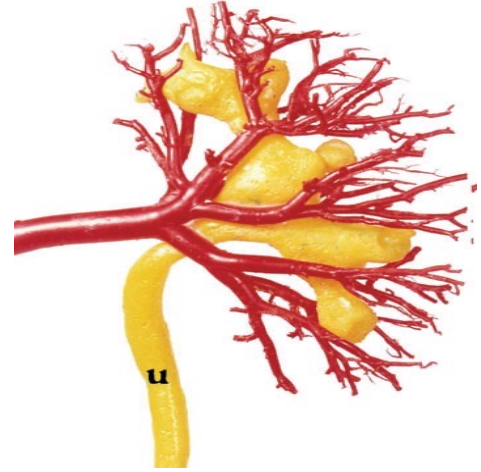
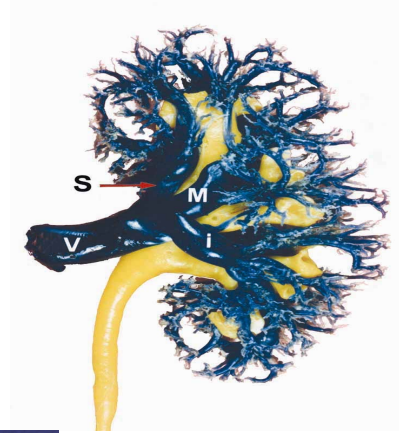
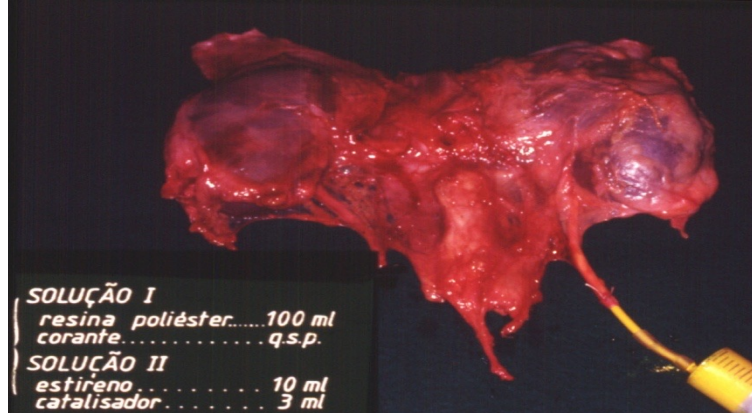
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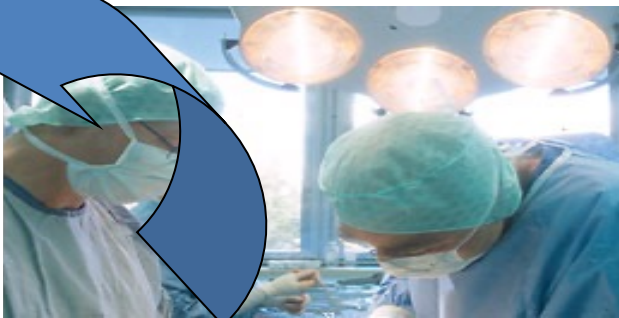
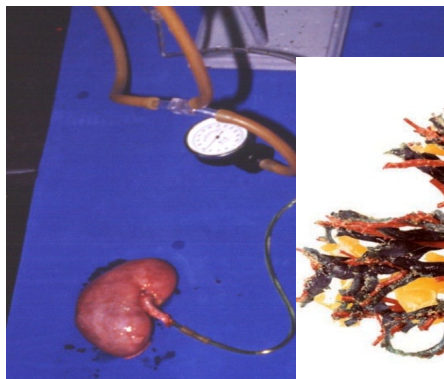
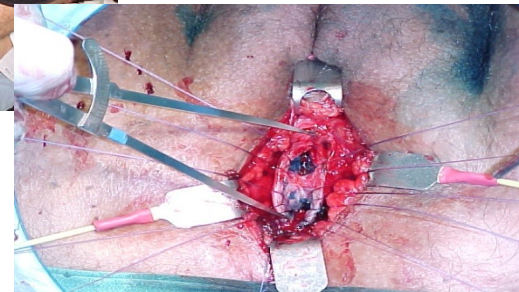
Basic and Clinical Research Applied to Urology

- Normal and Pathological Situations
- Humans: Adults, Children and Fetus
- Animal Models

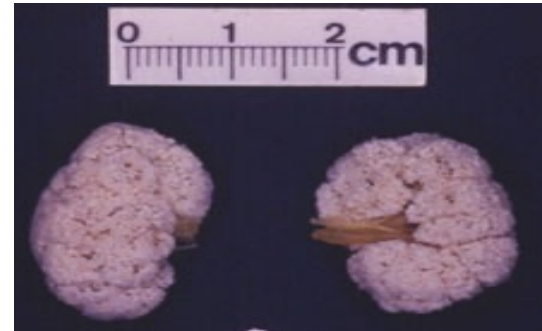
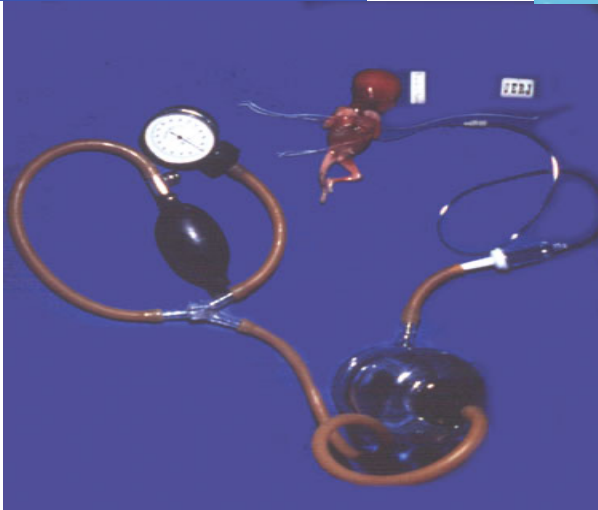
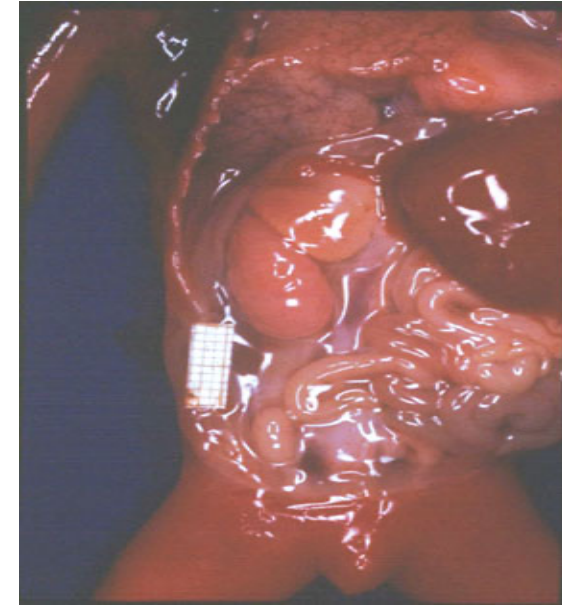
Translacional Research → Renal Applied to Urology



Translational Research Applied To reconstructive urology



Translational Research Applied to Pediatric Urology



- Kidney
- Penis
- Testis
- Urethra
- Prepuce

Study of Testis and Gubernaculum in Human Fetuses and Undescended Testis



- Fetuses without anomalies
- Prune Belly Syndrome
- Undescended Testis

Fetal Biometry



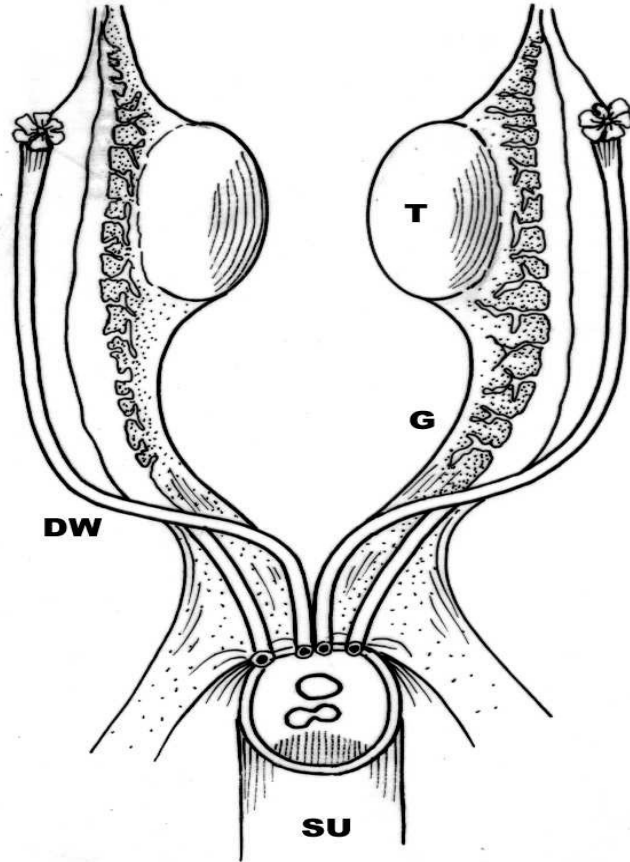
Total Length

VC Length

Weight

Foot length

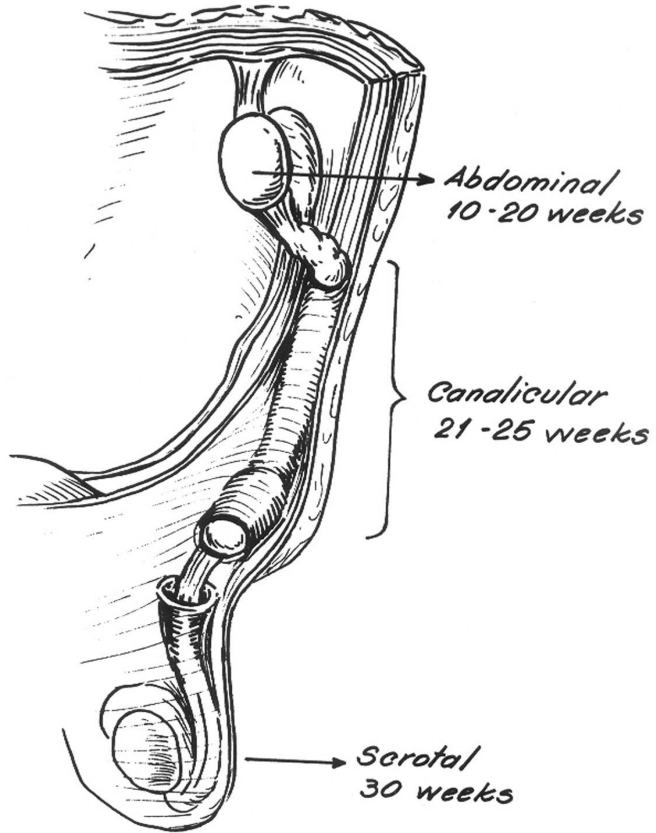
TESTICULAR MIGRATION



- Stage 1 – Transabdominal

- Stage 2 – Inguinoscrotal

STAGE 1- TRANSABDOMINAL



Testicular migration from the abdomen to the internal inguinal ring that begins around the 8th WPC and lasts until the 15th WPC

STAGE 2 - INGUINOSCROTAL



- Abdomen to Scrotum traversing abdominal wall between 17th to 30 weeks of gestation
- Gubernaculum: very important in this stage



ANALYSIS OF TESTICULAR MIGRATION DURING THE FETAL PERIOD IN HUMANS

FRANCISCO J. B. SAMPAIO* AND LUCIANO A. FAVORITO

From the Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil

ABSTRACT

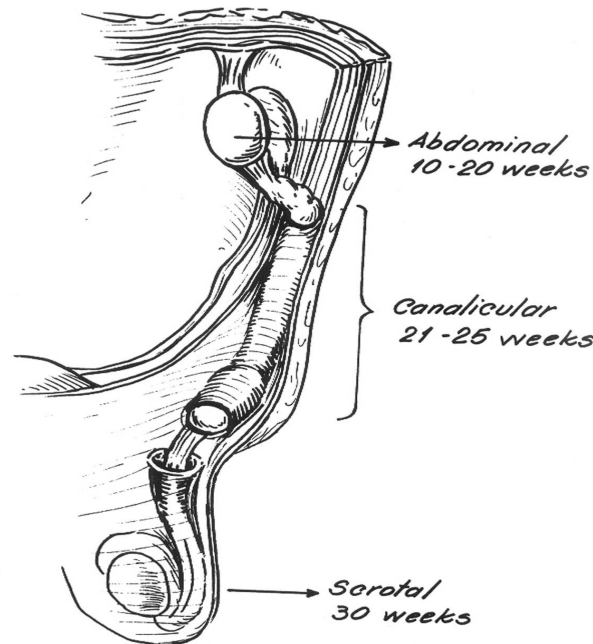
Purpose: We present an analysis concerning the testicular migration and its position correlated to body weight, crown-rump length and gestational age during the fetal period in humans without congenital abnormalities.

Materials and Methods: We studied bilaterally 142 testes taken from 71 fresh human fetuses between 10 and 35 weeks after conception. The fetuses were also evaluated in regard to crown-rump length and body weight. The position of the testes was correlated to the fetal parameters.

Results: In 37 fetuses (74 testes) at 10 to 23 weeks after conception only 7 testes (9.45%) had migrated from the abdomen and were situated in the inguinal canal, in 19 fetuses (38 testes) at 24 to 26 weeks after conception 22 testes (57.9%) had migrated from the abdomen and in 9 fetuses (18 testes) at 27 to 29 weeks after conception only 3 testes (16.7%) had not descended to the scrotum. The testes had not descended into the scrotum in any fetus weighing 990 gm. or less and with a crown-rump length of 24.5 cm. or less. On the other hand, in all fetuses weighing more than 1,220 gm. and with a crown-rump length of more than 27.5 cm. the testis was in the scrotum.

Conclusions: Until 23 weeks after conception the majority of testes remain in the abdomen. The more intense migration of the testes through the inguinal canal occurred between 21 and 25 weeks after conception. After 30 weeks after conception all testes were descended to the scrotum in all fetuses.

KEY WORDS: testis, fetus, anatomy



BODY WEIGHT	POSITION		
	ABDOMINAL	INGUINAL	SCROTAL
14 - 430 g	94.8%	5.2%	0
435 - 970 g	53.8%	46.2%	0
990 - 2530 g	6.25%	9.4%	84.35%
≥ 1200 g	0	0	100.0%



Urogenital Research Unit, State
University of Rio de Janeiro,
Brazil

Inguinoscrotal stage of testicular descent: analysis in 217 human fetuses

Tatiana S.C.G. Benzi, Waldemar S. Costa, Francisco J. Sampaio,
Luciano A. Favorito*



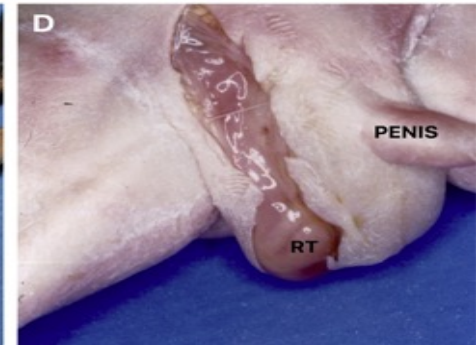
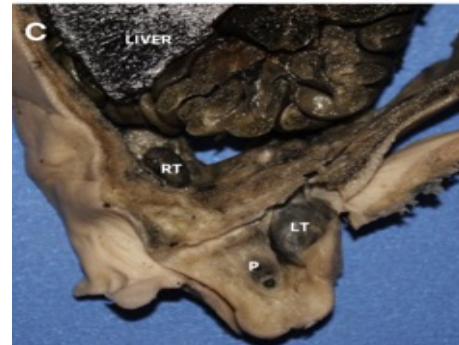
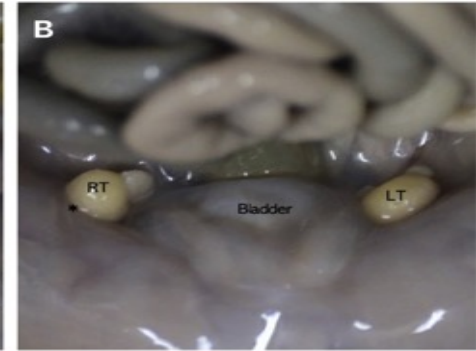
217 fetuses – 434 testes

329(75.8%) - abdominal, 48(11.05%) – inguinal
57(13.13%) - scrotal

We do not observe fetuses with less than 200g,
22.5cm of CRL and less than 17WPC with the
testis in inguinal canal

The first case of inguinal testis was observed in
a fetus with 17WPC, 203g and 15cm of CRL

All the fetuses with more than 30WPC had the
testis in scrotum.



Testicular migration chronology: do the right and the left testes migrate at the same time? Analysis of 164 human fetuses

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Luciano A. Favorito and Francisco J.B. Sampaio

Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil

Table 1 Data on the 164 fetuses (328 testes) studied divided by age groups (in WPC). For each group, the number and position of the testes studied and the position of the right testis (RT) and the left testis (LT) by group are shown.

Age, WPC	Number of fetuses (number of testes)	RT position, n (%) or n/N	LT position, n (%) or n/N	RT and LT position, n (%) or n/N
12–15	30 (60)	Abdomen, 30 (100) Inguinal, 0 Scrotum, 0	Abdomen, 30 (100) Inguinal, 0 Scrotum, 0	Abdomen, 60 (100) Inguinal, 0 Scrotum, 0
16–20	42 (84)	Abdomen, 41 (97.6) Inguinal, 1 (2.4) Scrotum, 0	Abdomen, 42 (100) Inguinal, 0 Scrotum, 0	Abdomen, 83 (98.8) Inguinal, 1 (1.2) Scrotum, 0
21–25	55 (110)	Abdomen, 42 (76.4) Inguinal, 12 (21.8) Scrotum, 1 (1.8)	Abdomen, 41 (74.5) Inguinal, 13 (23.6) Scrotum, 1 (1.8)	Abdomen, 83 (75.5) Inguinal, 25 (22.7) Scrotum, 2 (1.8)
26–30	25 (50)	Abdomen, 3 (12) Inguinal, 1 (4) Scrotum, 21 (84)	Abdomen, 4 (16) Inguinal, 2 (8) Scrotum, 19 (76)	Abdomen, 7 (14) Inguinal, 3 (6) Scrotum, 40 (80)
31–35	12 (24)	Abdomen, 0 Inguinal, 1/12 Scrotum, 11/12	Abdomen, 0 Inguinal, 0 Scrotum, 12/12	Abdomen, 0 Inguinal, 1 (4.2) Scrotum, 23 (95.8)
Total	164 (100)	Abdomen, 116 (70.7) Inguinal, 15 (9.1) Scrotum, 33 (20.1)	Abdomen, 117 (71.3) Inguinal, 15 (9.1) Scrotum, 32 (19.5)	Abdomen, 233 (71) Inguinal, 30 (9.1) Scrotum, 65 (19.8)

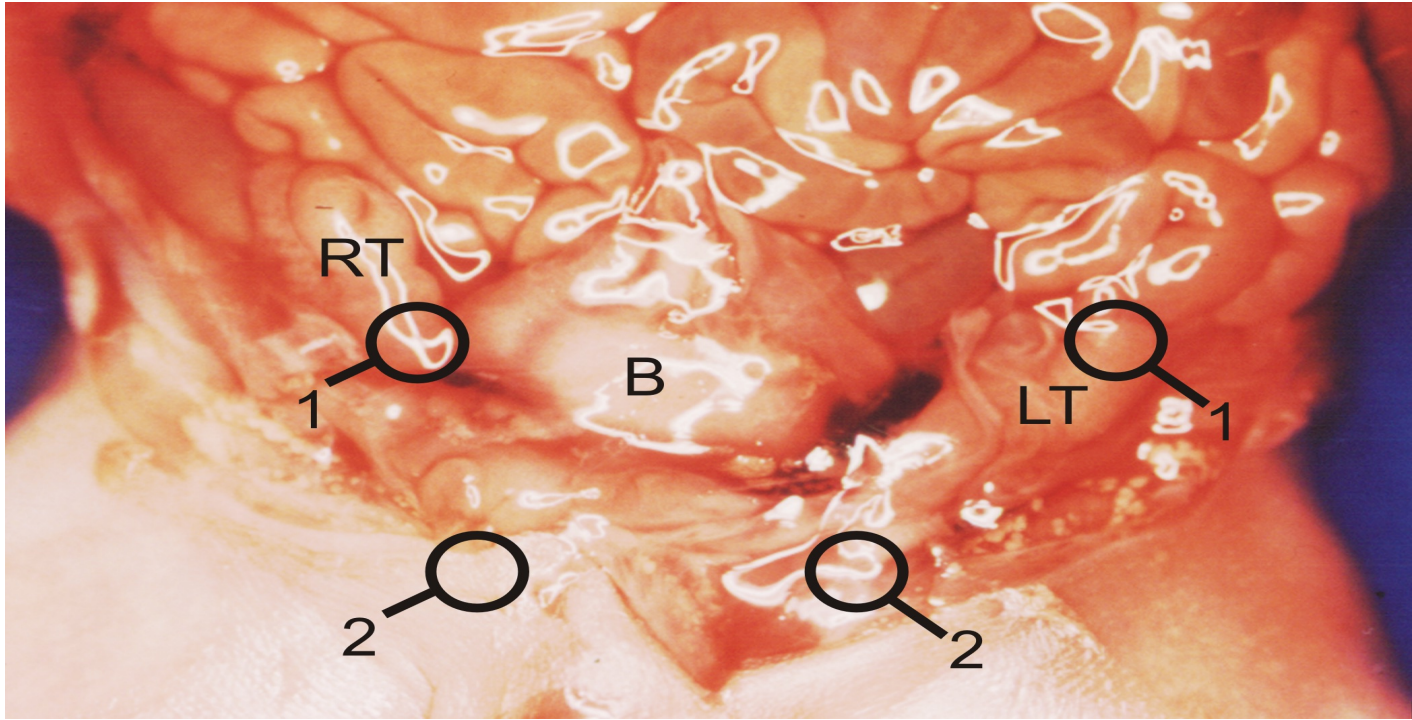
Table 2 Position of the testes of the nine fetuses with asymmetric testicular migration. In five of the nine cases, the right testicle is located in a lower position than the left.

Age, WPC	Weight, g	V-C, cm	RT	LT
18	264	16	Inguinal	Abdomen
23	626	22	Scrotum	Abdomen
25	741	23	Abdomen	Scrotum
25	751	24	Inguinal	Scrotum
25	750	25	Scrotum	Inguinal
26	805	24	Inguinal	Abdomen
27	1029	26	Abdomen	Scrotum
28	1220	27	Inguinal	Abdomen
31.4	1420	34	Inguinal	Scrotum

V-C, vertex-coccyx length; RT, right testicle; LT, left testicle.

9 Cases of Assymetric testicular (2.7%)





Assymetric Testicular Migration – Rare Situation

TESTICULAR MIGRATION

» SEVERAL FACTORS:

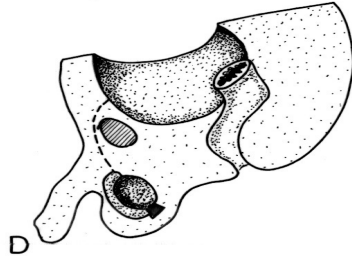
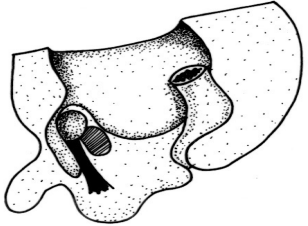
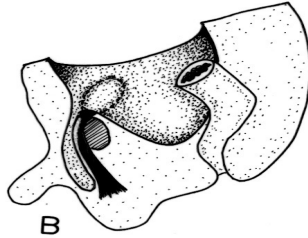
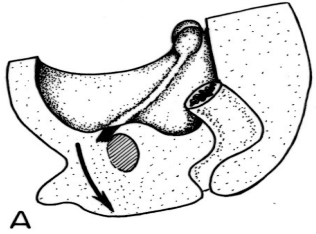
» HORMONAL STIMULI

» INTRA ABDOMINAL PRESSURE

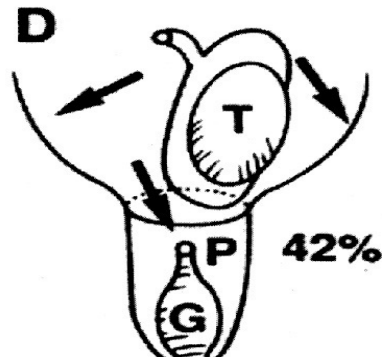
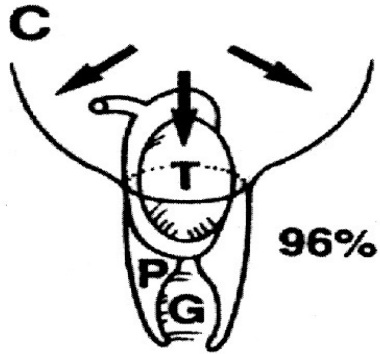
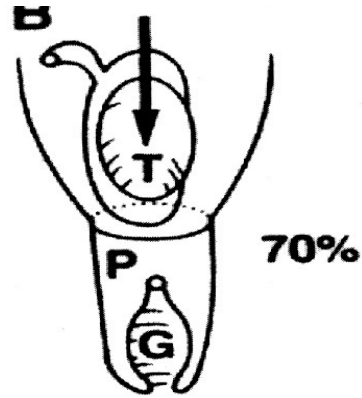
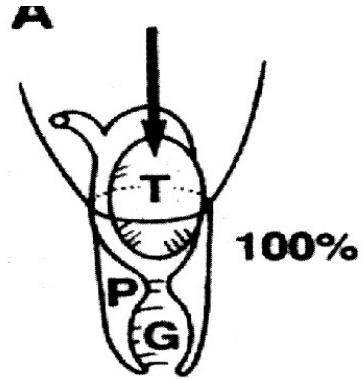
» DEVELOPMENT OF INGUINAL CANAL AND
PROCESSUS VAGINALIS

» STIMULUS FROM GENITOFEMORAL NERVE

» DEVELOPMENT OF THE GUBERNACULUM



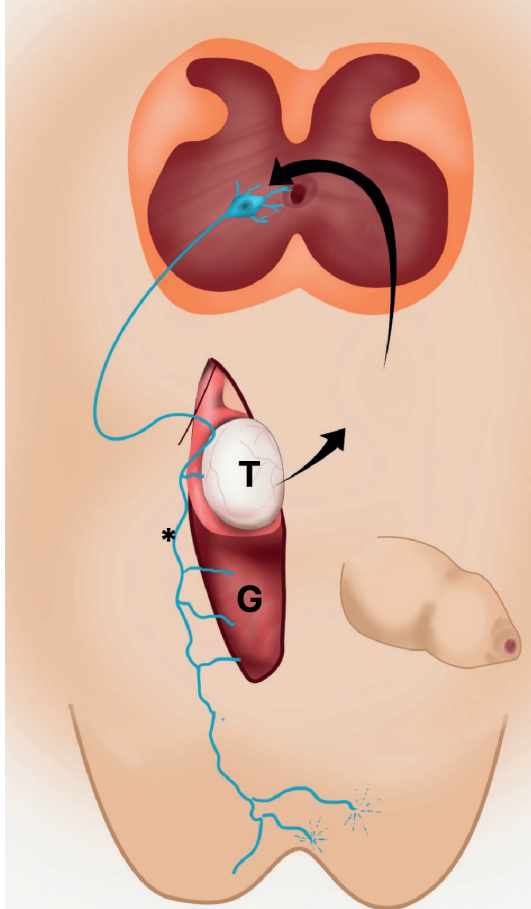
INTRA-ABDOMINAL PRESSURE



» Adjuvant Factor

» D – Abdominal Wall And
Gubernacular transection
– Low Migration

STIMULUS FROM GENITO-FEMORAL



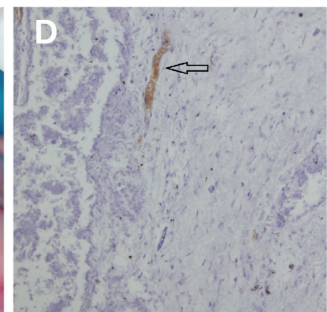
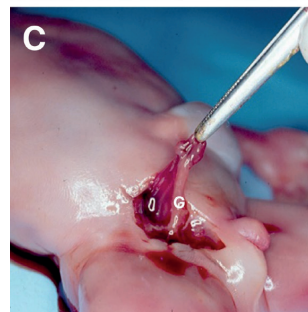
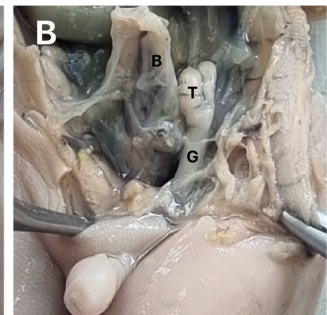
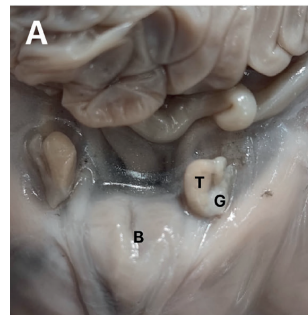
- » **GFN – Second Messenger for ANDROGEN by release of Calcitonin gene-related peptide (CGRP)**
- » **GFN contain CGRP**
- » **CGRP – Rhythmic contractions of the gubernaculum**



Role of Gubernaculum testis invagination during the process of testicular migration in human fetuses

Luciano A. Favorito¹, Laura M. M. Favorito¹, Ana R. M. Moraes¹, Francisco J. B. Sampaio¹

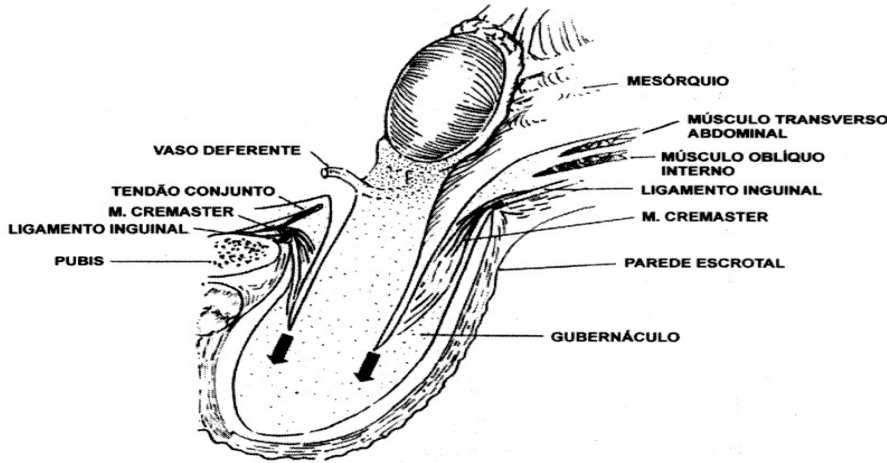
¹ Unidade de Pesquisa Urogenital, Departamento de Anatomia da Universidade do Estado do Rio de Janeiro – UERJ, Rio de Janeiro, RJ, Brasil



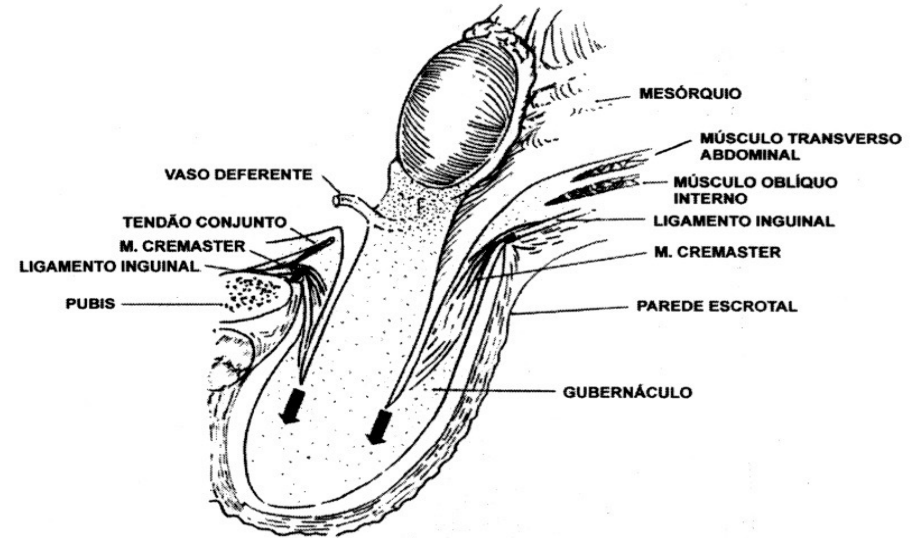
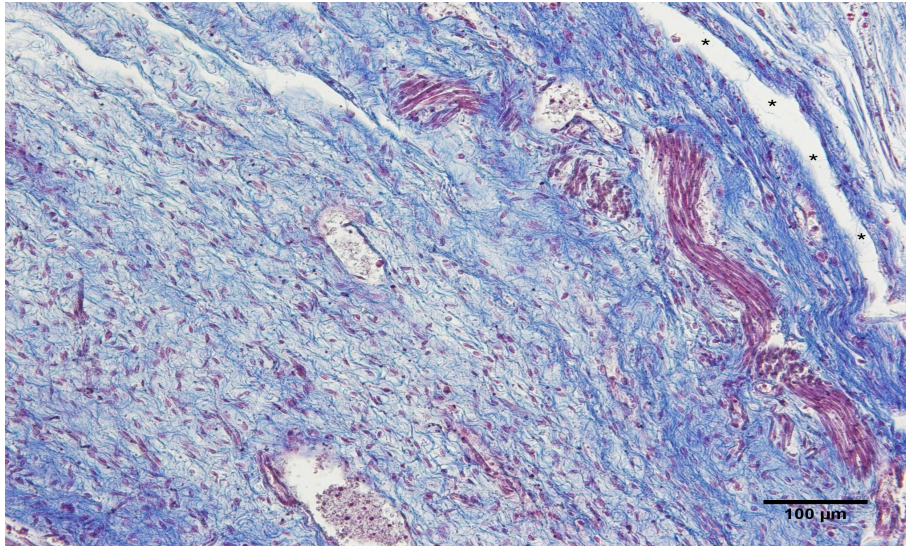
INGUINAL CANAL AND PROCESSUS VAGINALIS

» Gubernaculum underwent a swelling reaction through the inguinal canal to create the processus vaginalis

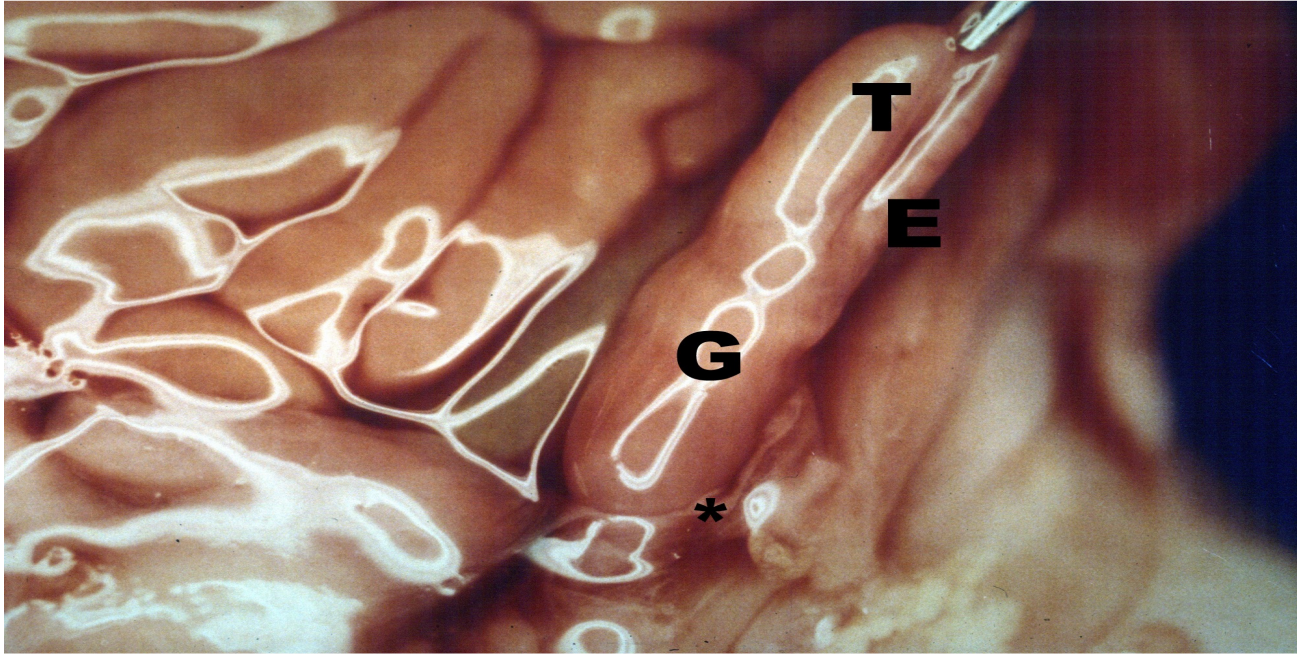
» The cremaster muscle developed in the outer rim of the proximal gubernaculum outside PV



PROCESSUS VAGINALIS

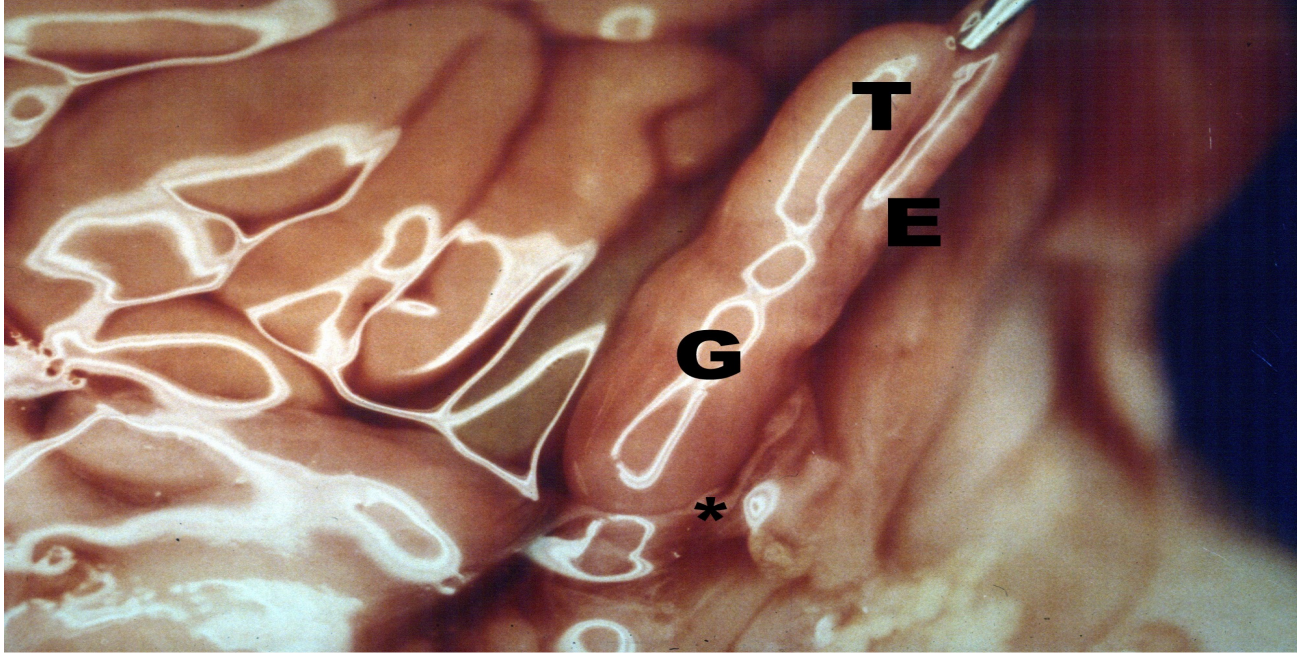


GUBERNACULUM



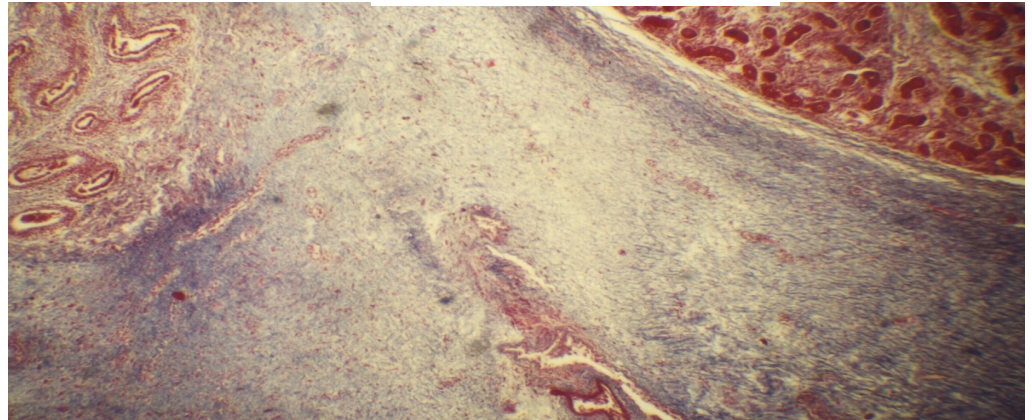
- **Most Important Structure in Testicular Migration**
- **Morphological changes during the human fetal period**

GUBERNACULUM



- » ELONGATED AND CYLINDRICAL MESENCHYMAL STRUCTURE
- » EXPANDS INGUINAL CANAL AND PULLS THE TESTIS
- » CONNECTS THE INFERIOR POLE OF THE TESTIS AND THE TAIL OF EPIDIDYMIS TO THE SCROTUM

PROXIMAL GUBERNACULUM



PROXIMAL INSERTION OF GUBERNACULUM TESTIS IN NORMAL HUMAN FETUSES AND IN BOYS WITH CRYPTORCHIDISM

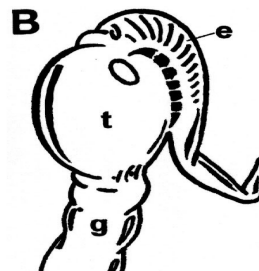
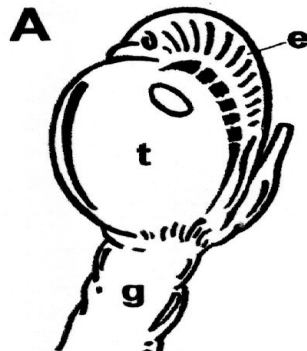
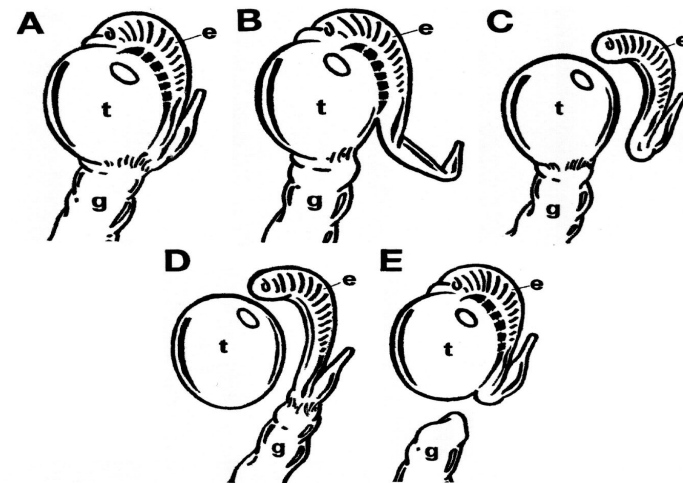
LUCIANO A. FAVORITO, FRANCISCO J. B. SAMPAIO,* VALTER JAVARONI,
 LUIZ E. MACEDO CARDOSO AND WALDEMAR S. COSTA

From the Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil

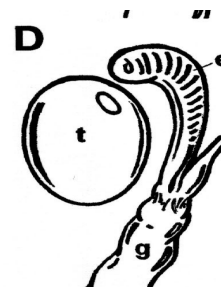
ABSTRACT

Purpose: We determine how the proximal gubernaculum testis is attached to the testis and epididymis in human fetuses, and compare these data with findings in boys who had undergone surgery for cryptorchidism.

Materials and Methods: We analyzed 280 testes and epididymides with the gubernacula of 140 well preserved, fresh human fetuses ranging from 10 to 35 weeks after conception with no detectable congenital malformations and 36 undescended testes of 28 boys 2 to 15 years old (mean age 6.8) who had undergone surgery for cryptorchidism. In both groups the different conformations of the relationship among the proximal gubernaculum, testis and epididymis were classified according to a system used for patients with cryptorchidism. In group A the gubernaculum is attached to the testis and epididymis, in group B the gubernaculum is attached only to the testis with a tail disjunction epididymal anomaly, in group C the gubernaculum is attached only to the testis with total disjunction of the epididymis, in group D the gubernaculum is attached only to the epididymal tail and in group E there are no attachments among gubernaculum, testis and epididymis.

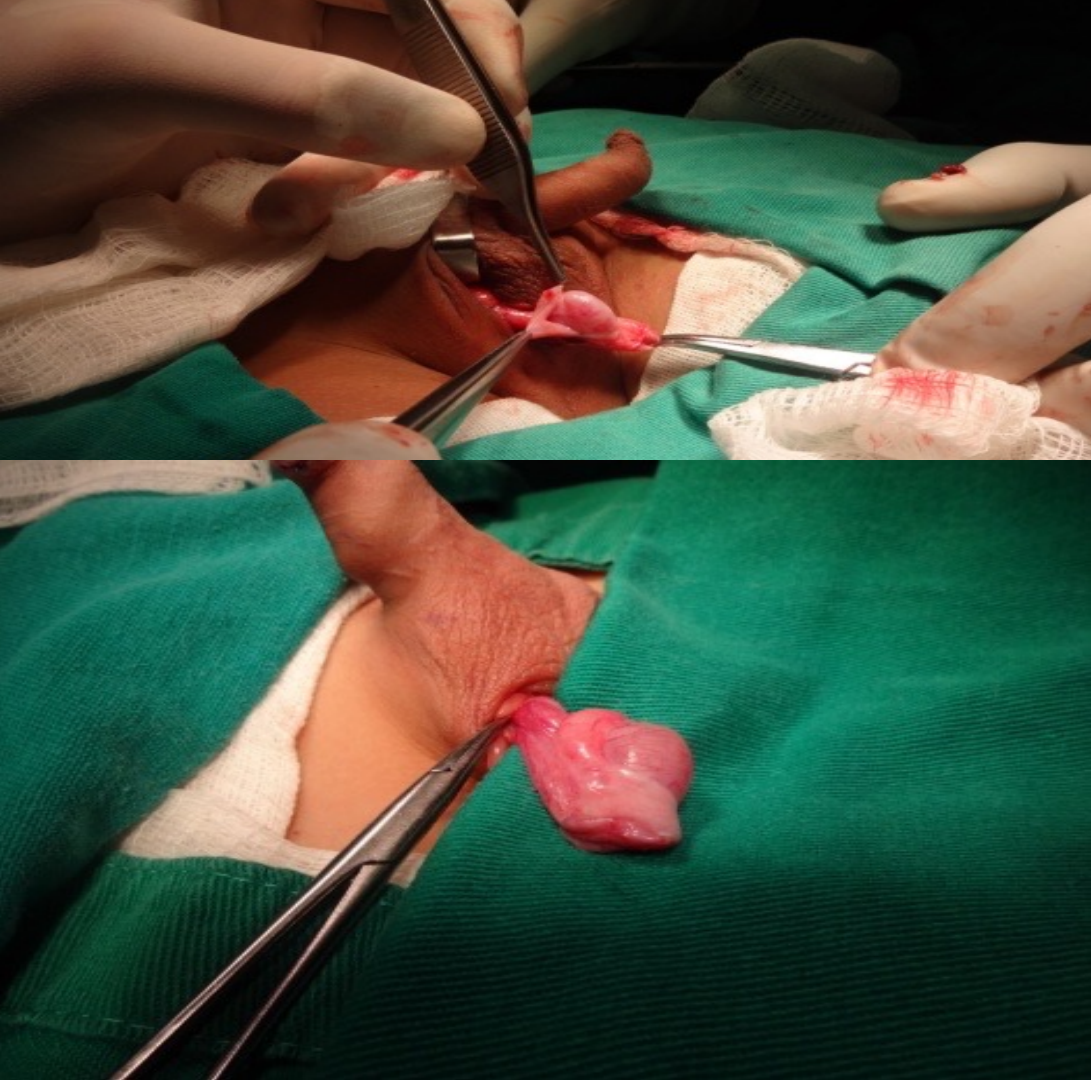


1.2% normal fetuses
 22.2% cryptorchidic

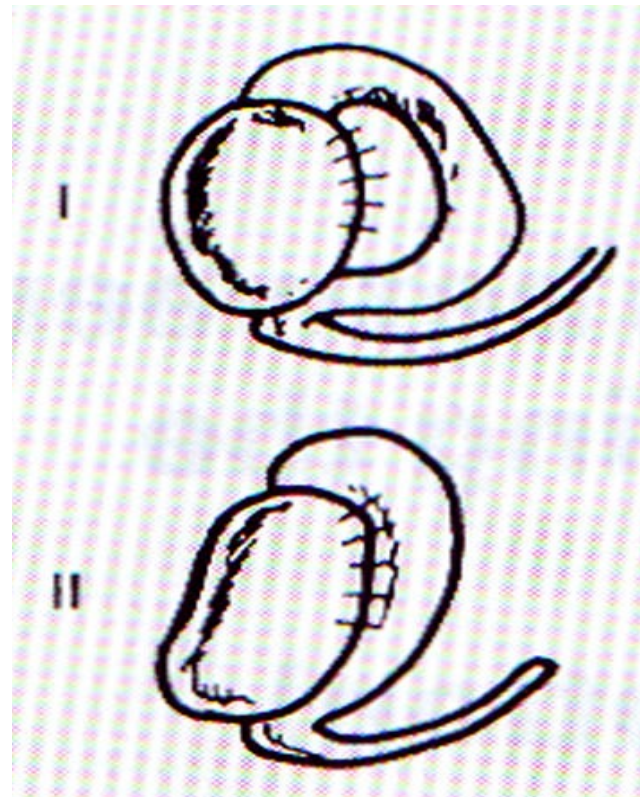


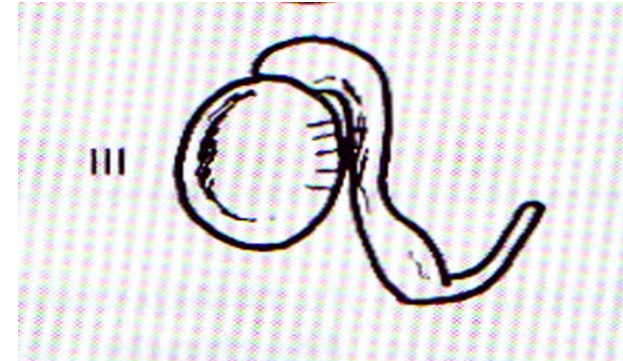
5.6% cryptorchidic

98.8% normal fetuses
 72.2% cryptorchidic

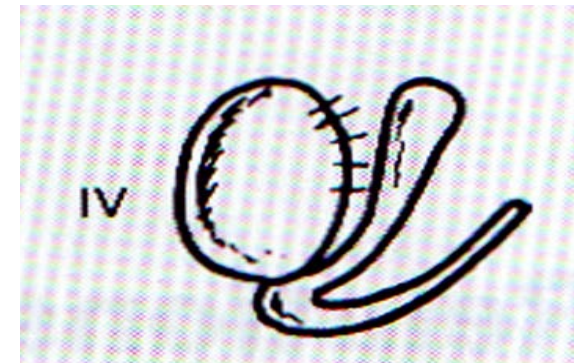


Normal Relationship



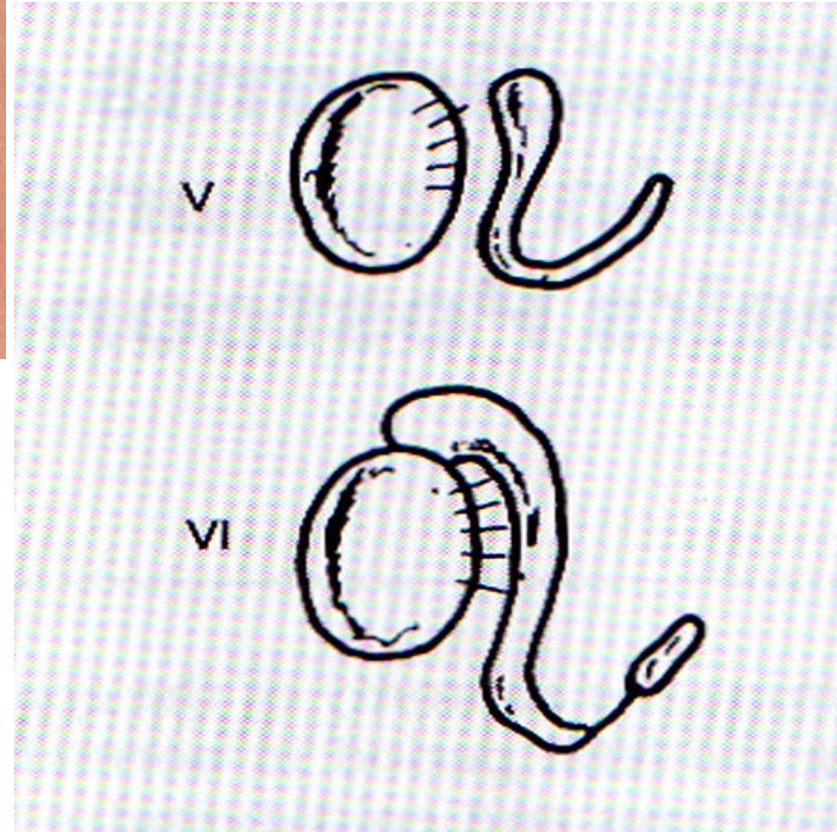


Disjunction Anomalies





Disjunction and obstruction



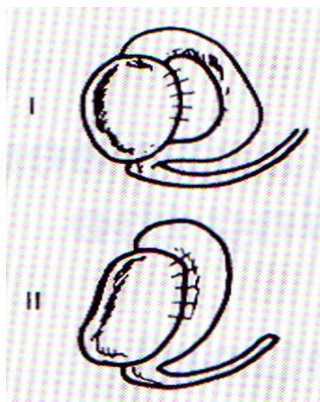
Anatomical Relationships between Testis and Epididymis during the Fetal Period in Humans (10–36 Weeks Postconception)

Key Words

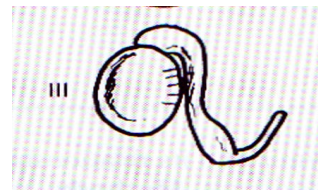
Testis
Epididymis
Abnormalities
Fetus
Anatomy
Development

Abstract

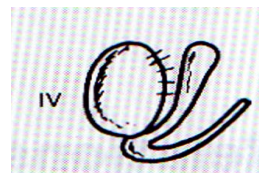
Objective: To determine the anatomy of the epididymis and its relationship with the testis during the fetal period in normal individuals. **Methods:** We studied bilaterally 146 testes and epididymides taken from 73 normal fresh human fetuses ranging in age from 10 to 36 weeks postconception. The epididymal anatomy was classified in six types: type I: the epididymis is connected to the testis by its head and tail and the epididymal body is separated from the testis; type II: the epididymis is completely attached to the testis; type III: the



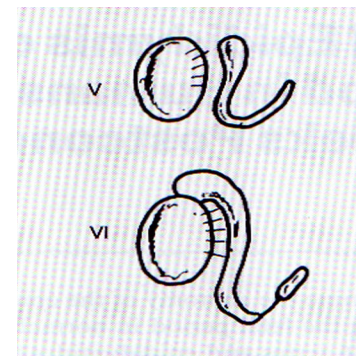
89.7%



2.05%



0.68%



0%

Normal = 97.25%

GUBERNACULUM DISTAL PORTION



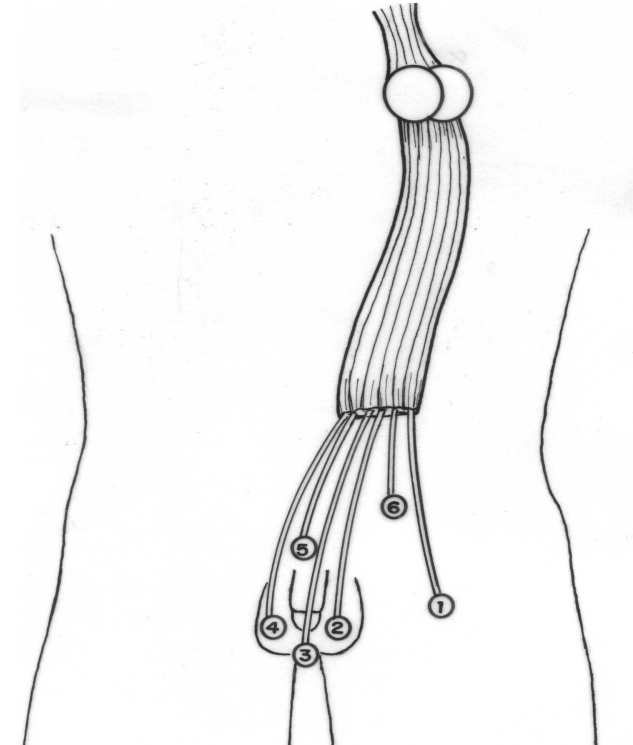
GUBERNACULUM DISTAL PORTION

- 1 – Femoral
- 2 - Scrotal
- 3 - Perineal
- 4 - Contralateral Hemi-Scrotum
- 5 – Pubopenile
- 6 - Abdominal Wall
(Interstitial)

Testicular Ectopie



Multiple distal insertions



IS THERE A RELATIONSHIP WITH ANOMALOUS INSERTIONS OF THE DISTAL GUBERNACULUM TESTIS AND TESTICULAR ECTOPIA? ANALYSIS IN HUMAN FETUSES AND PATIENTS WITH CRYPTORCHIDISM

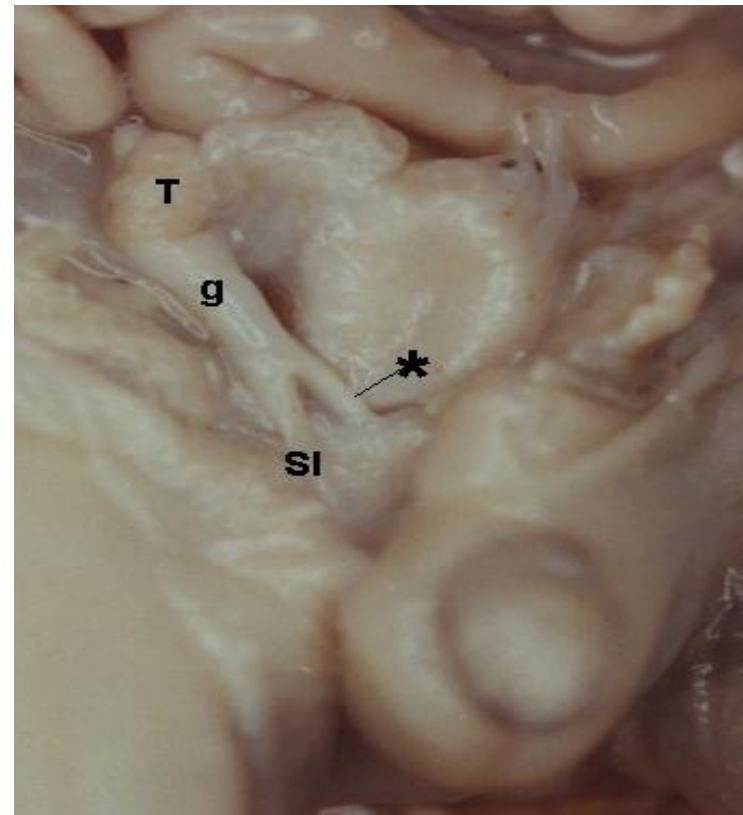
LUCIANO A. FAVORITO, CARLOS A. B. KLOJDA, WALDEMAR S. COSTA
AND FRANCISCO J. B. SAMPAIO*

From the Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil

ABSTRACT

Purpose: One of the most accepted theories for explaining testicular ectopia is the existence of multiple distal insertions of the gubernaculum testis. We studied the distal insertions of the gubernaculum in human fetuses and patients with cryptorchidism.

Materials and Methods: We studied 326 gubernacula in 163 human fetuses at 10 to 35 weeks of gestation and 133 gubernacula in 101 patients with cryptorchidism (mean age 6.4 years). With the aid of a stereoscopic microscope (2.5× magnification), the existence of distal insertions of the



- Fetuses- 324 gubernaculum
Only 2 (0.6%) – Pubo-penile

Undescended Testis

120 Gubernaculum – Without anomalies

STRUCTURE OF FETAL GUBERNACULUM IN HUMAN FETUSES

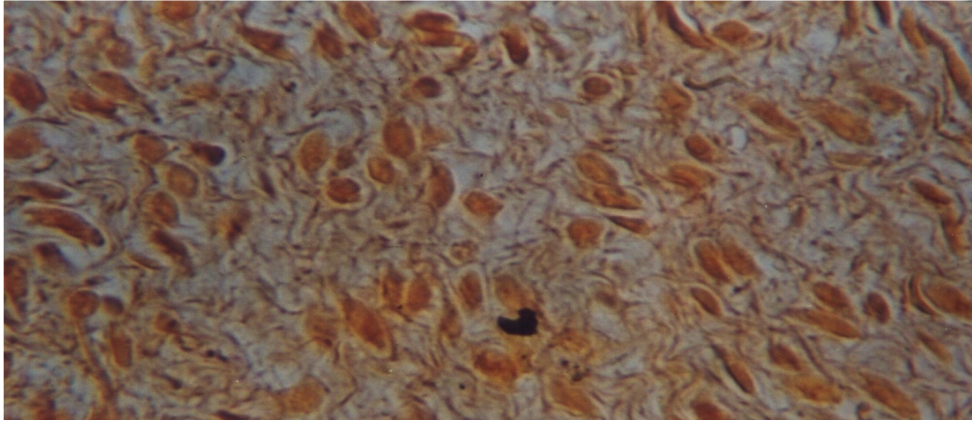
» ELASTIC FIBERS

» COLLAGEN

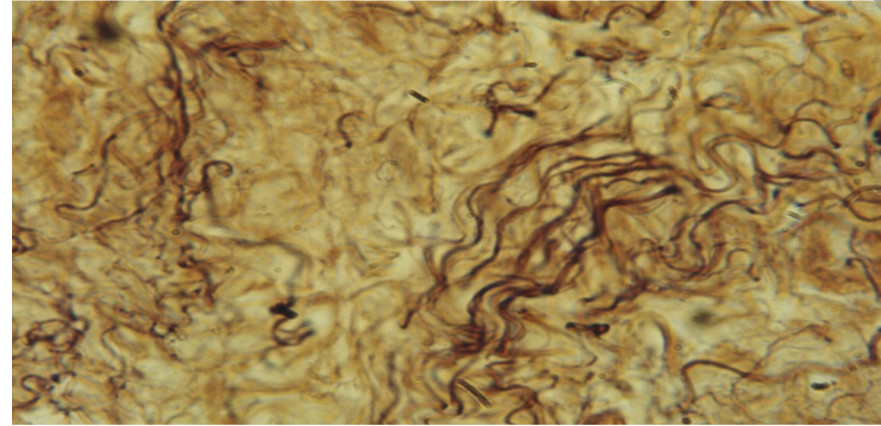
» MUSCLE

» GAGS

ELASTIC FIBERS



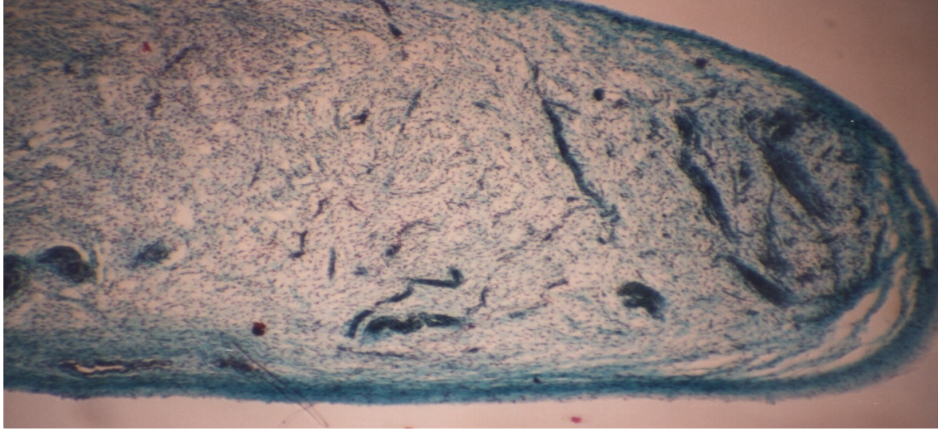
15 WPC



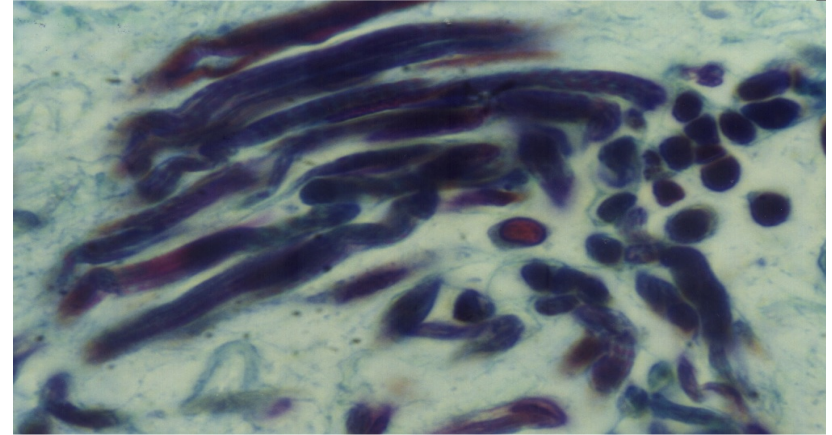
28 WPC

- » Concentrated at the distal end
- » Appeared only later in testicular descent
- » Gubernaculum becomes an essentially fibrous structure

MUSCLE CELLS



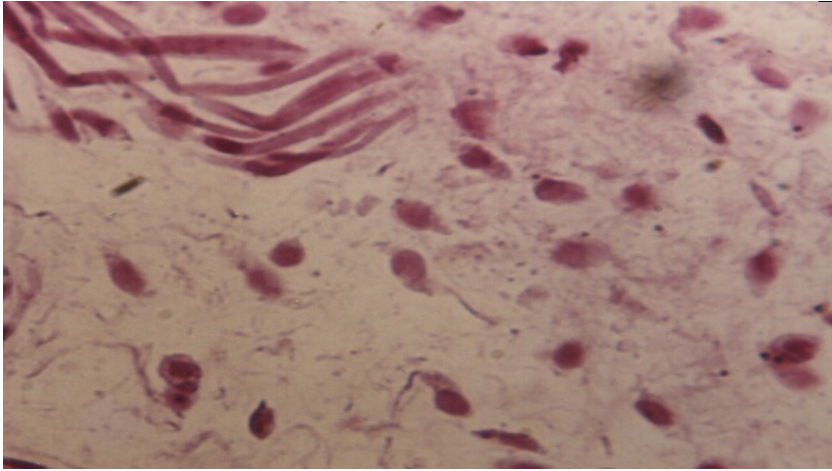
15 WPC



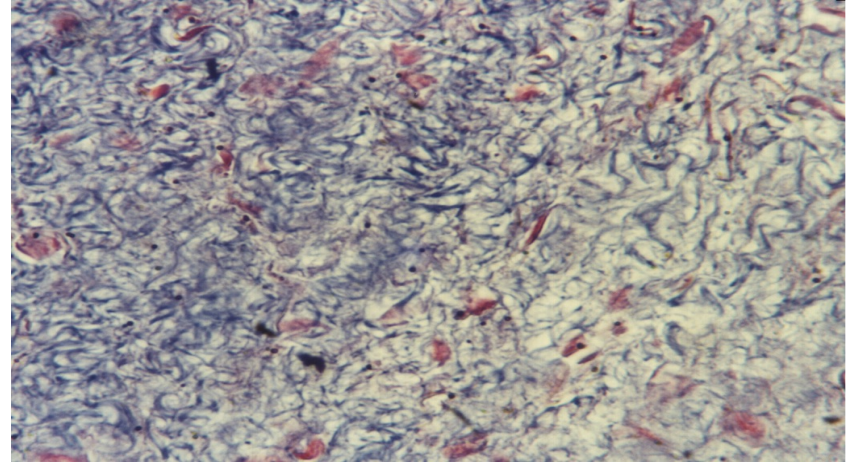
24 WPC

- » Overall paucity of muscle cells
- » Striated muscle cells were sparse
- » Gubernaculum should not be capable of contraction?

COLLAGEN



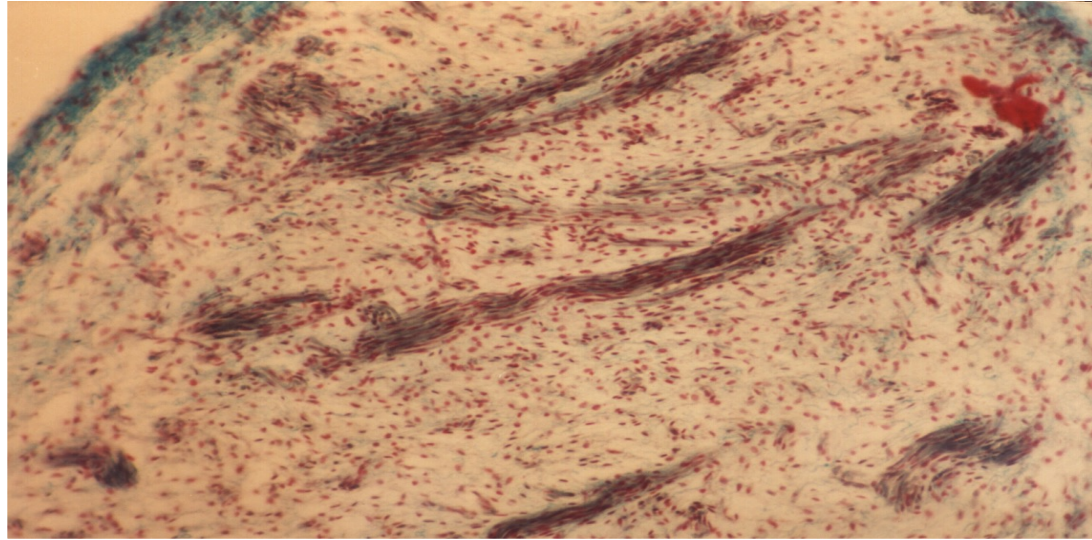
15 WPC



27 WPC

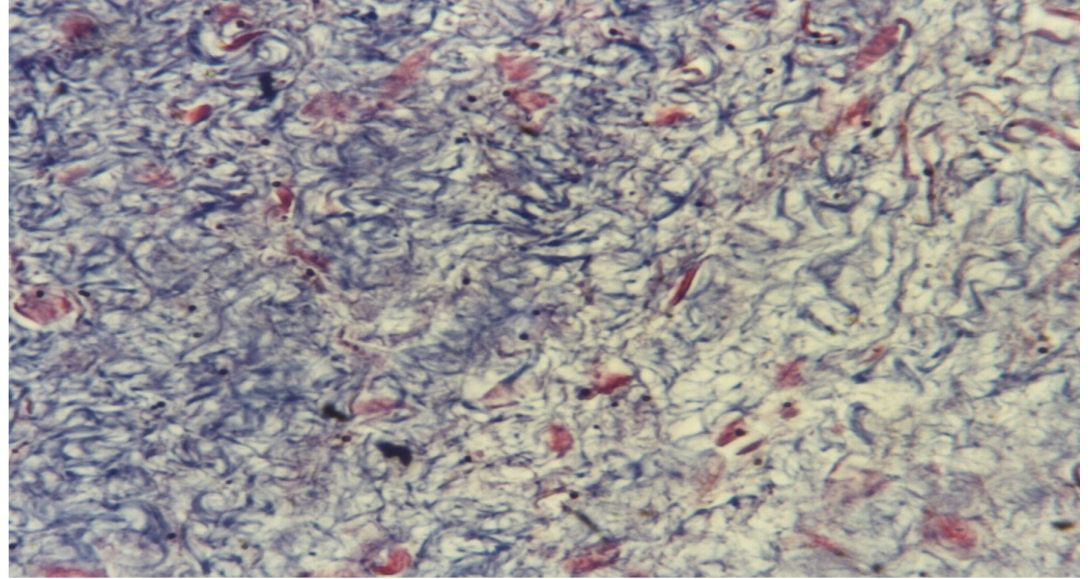
- » Early phases – loose extracellular matrix and numerous fibroblasts
- » Scrotum – Progressively fibrous with low cellularity – Increases collagen

ABDOMINAL GUBERNACULUM



Earlier in testicular descent the gubernaculum is more hydrated and less fibrous, and subsequently undergoes extensive remodeling.

SCROTAL GUBERNACULUM



- Decrease in its volume and length
- Essentially a fibrous structure
- Densely packed collagen fibers interspersed with separated fibroblast-like cells

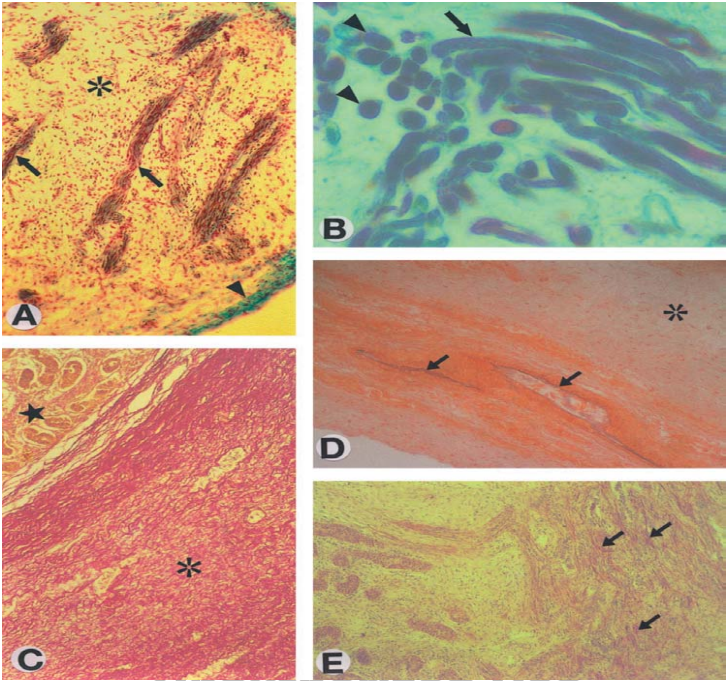
TESTICULAR MIGRATION: REMODELING OF CONNECTIVE TISSUE AND MUSCLE CELLS IN HUMAN GUBERNACULUM TESTIS

WALDEMAR S. COSTA, FRANCISCO J. B. SAMPAIO,* LUCIANO A. FAVORITO AND LUIZ E. M. CARDOSO

From the Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil

The position of the testis and fetal parameters

No. Gestational Wks.	Wt. (gm.)	Crown/Rump Length (cm.)	Rt. Testis	Lt. Testis
15	170	15	Abdominal	Abdominal
15	225	17	Abdominal	Abdominal
16	190	14	Abdominal	Abdominal
20	381	18	Abdominal	Abdominal
20	468	18	Abdominal	Abdominal
20	371	19	Abdominal	Abdominal
24	865	25	Canalicular	Canalicular
24	660	20	Abdominal	Abdominal
25	698	23	Abdominal	Abdominal
28	1,415	36.5	Scrotal	Scrotal
28	1,291	27.5	Scrotal	Scrotal
29	1,190	27	Scrotal	Scrotal



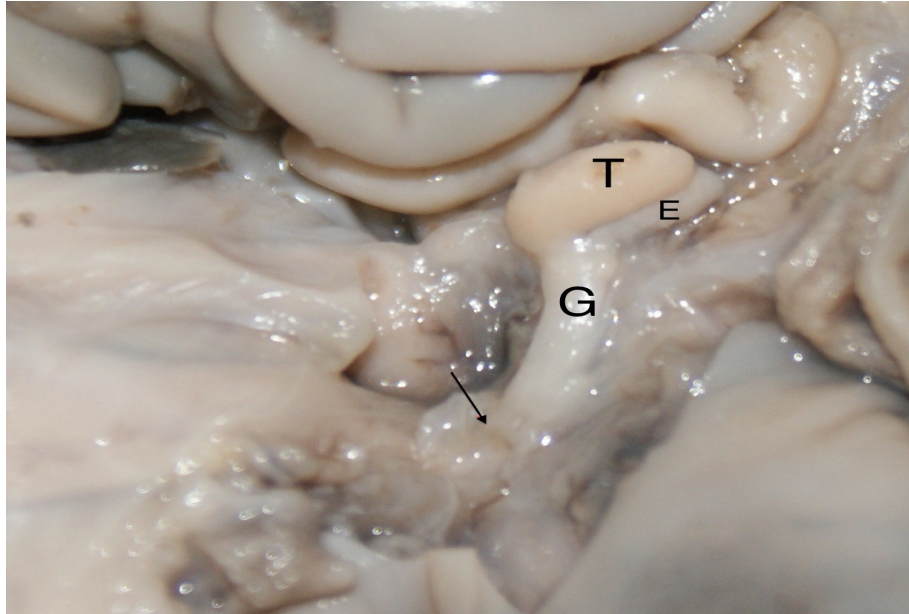
GUBERNACULUM TESTIS AND PRUNE-BELLY SYNDROME



Disorder characterized by:

- Deficiency of the abdominal muscles,
- Malformations of the urinary tract
- Bilateral cryptorchidism.

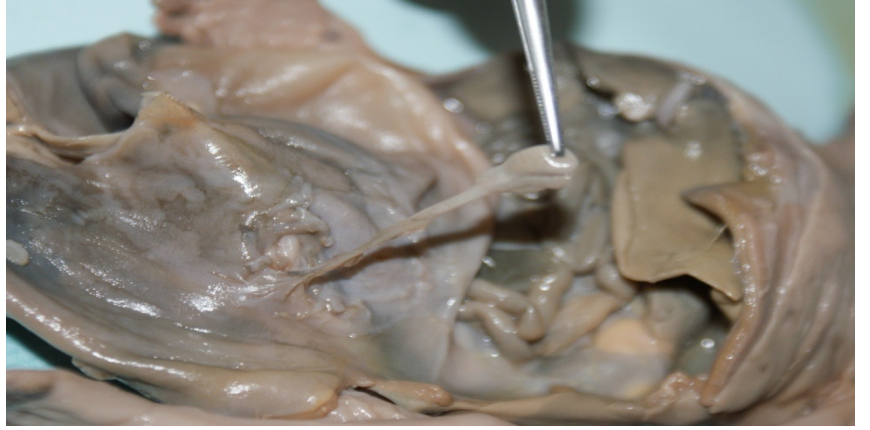
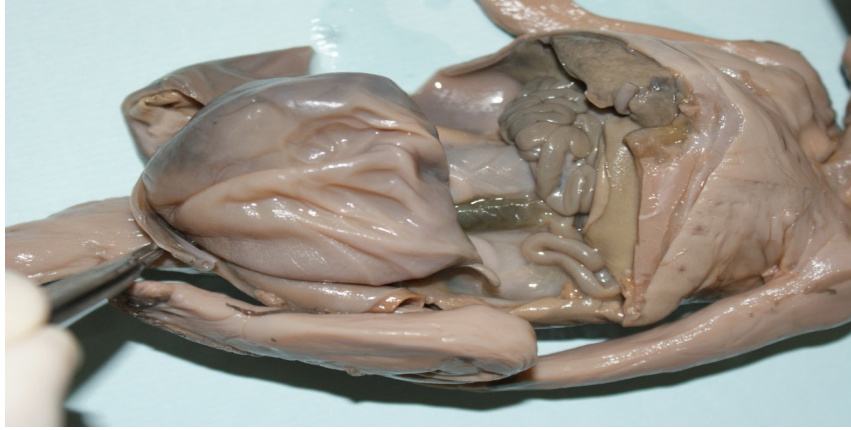
GUBERNACULUM TESTIS AND PRUNE-BELLY SYNDROME



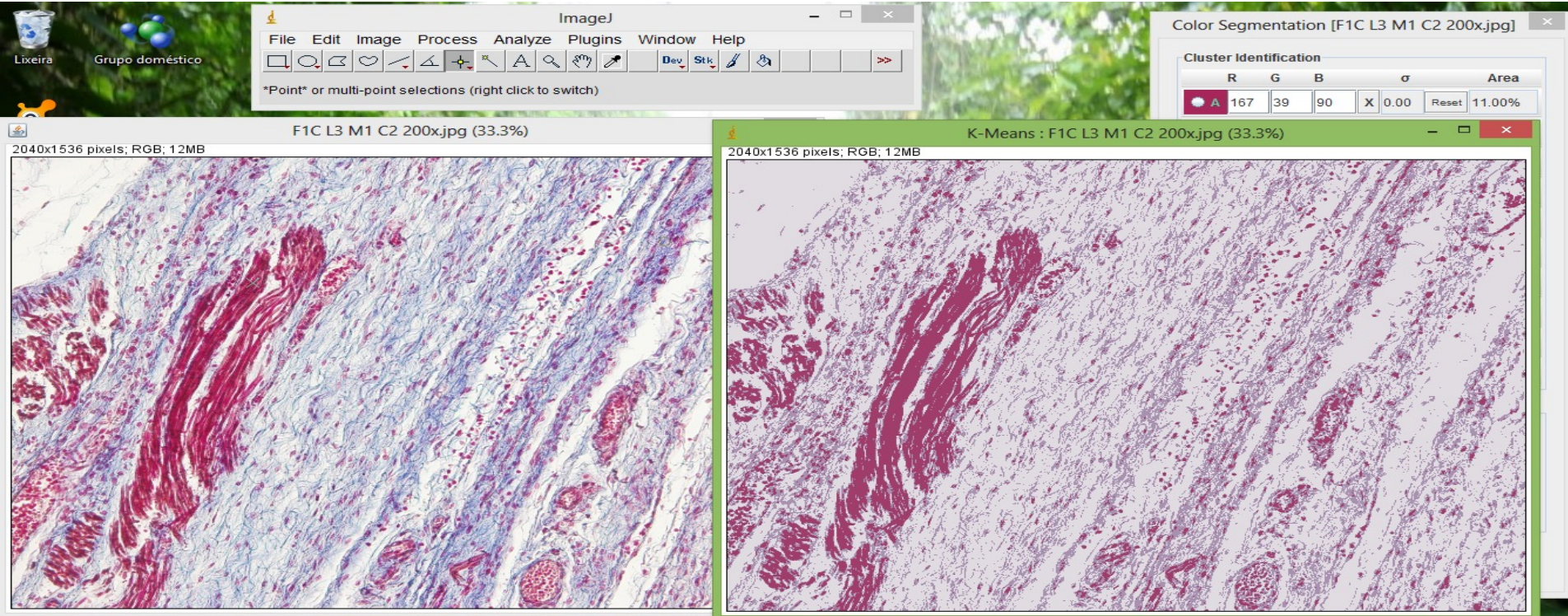
Increased intraabdominal pressure in PBS causes alterations in gubernacular structure?

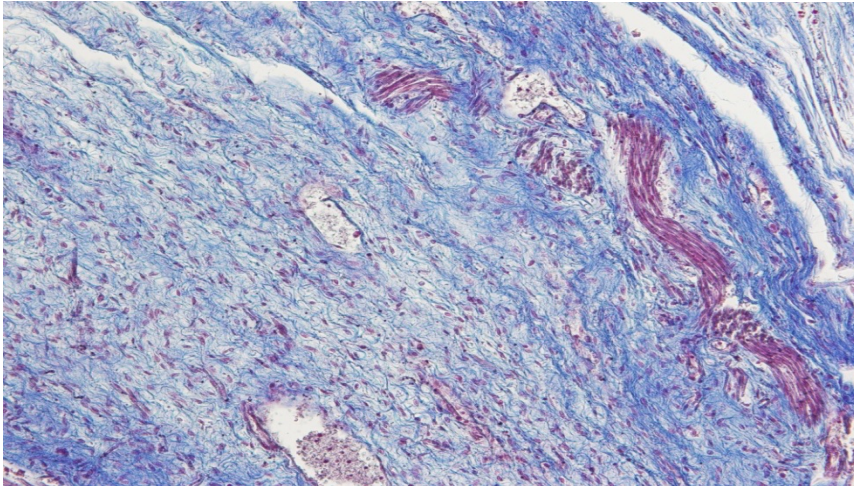
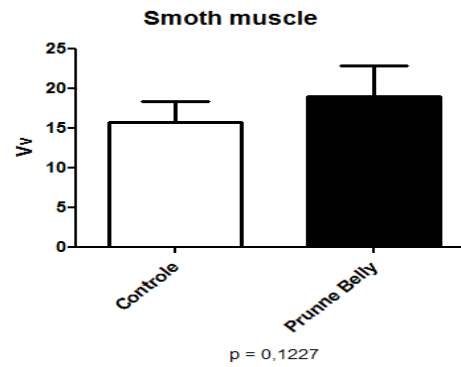
» We studied 7 fetuses without anomalies and 3 fetuses with Prunne Belly syndrome.



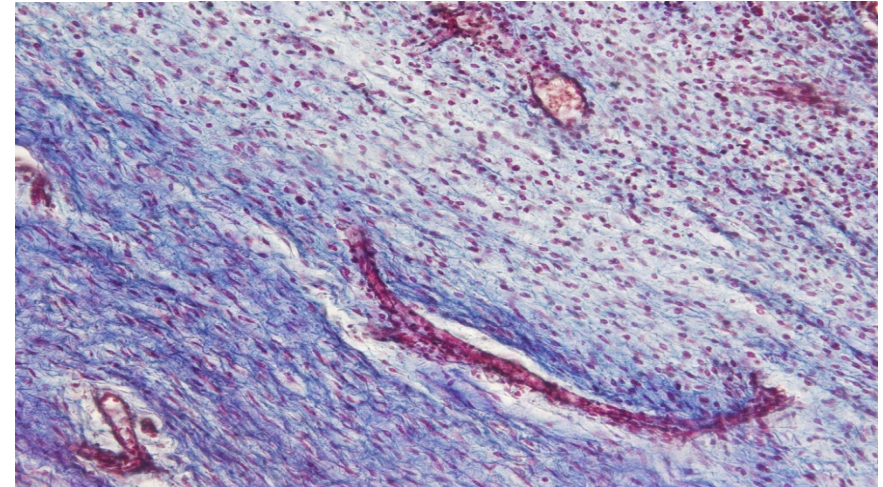


» The morphometric analysis was evaluated using the software Image J.

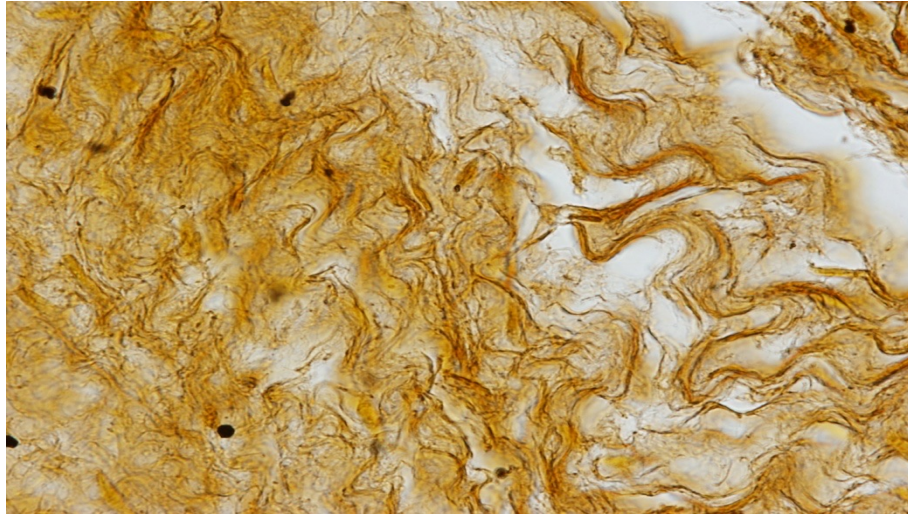
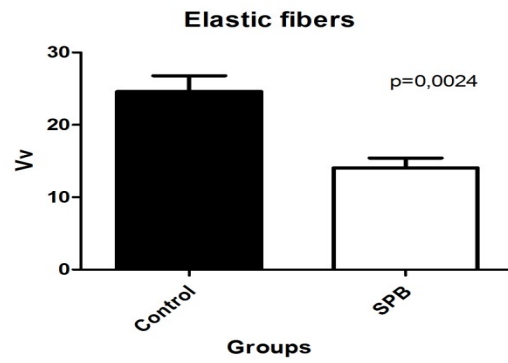




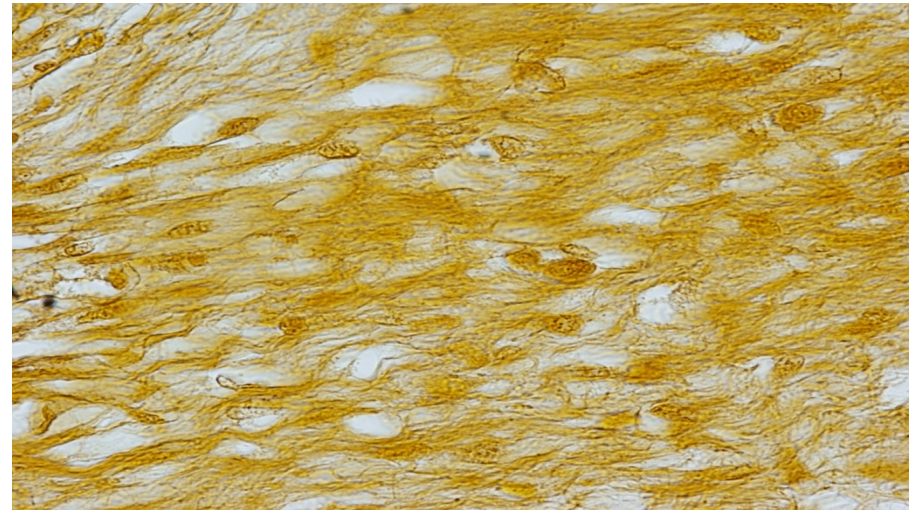
Control, 21 WPC. 200x



Prunne Belly, 23 WPC. 200x



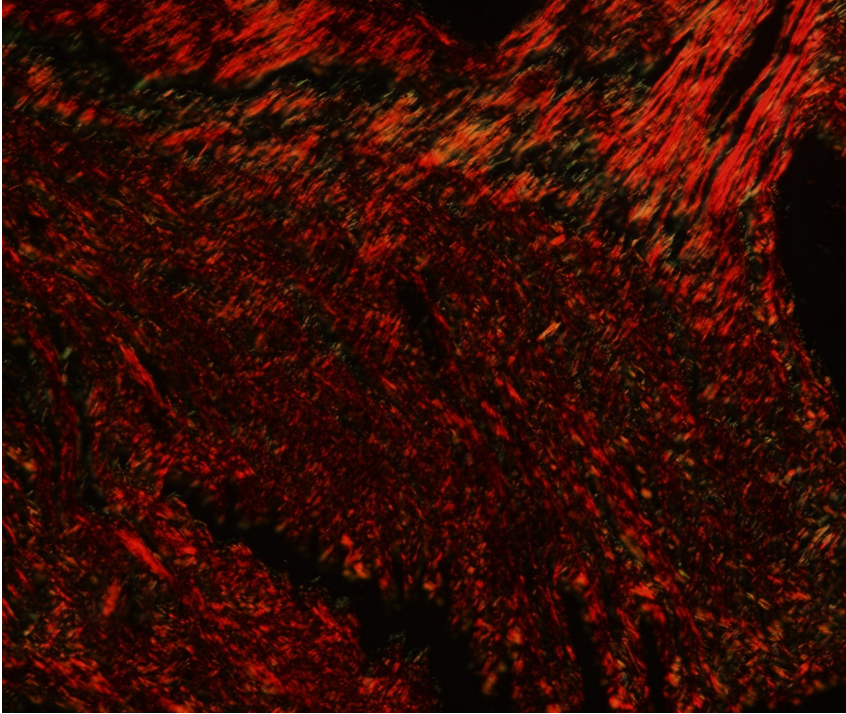
Control, 21 WPC. 200x



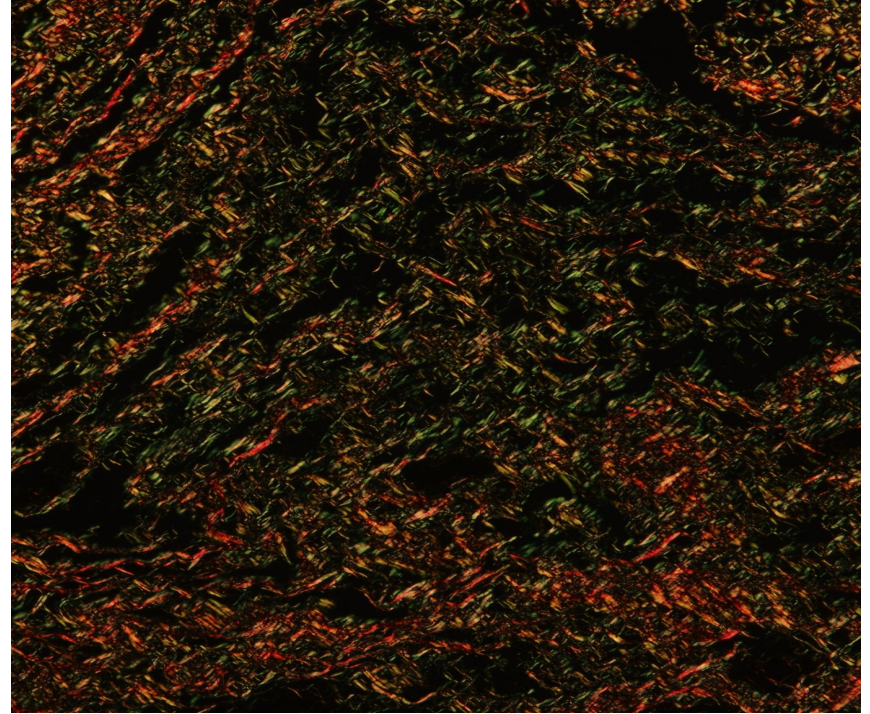
Prunne Belly, 23 WPC. 200x

COLLAGEN

PBS – Predominance of Collagen III

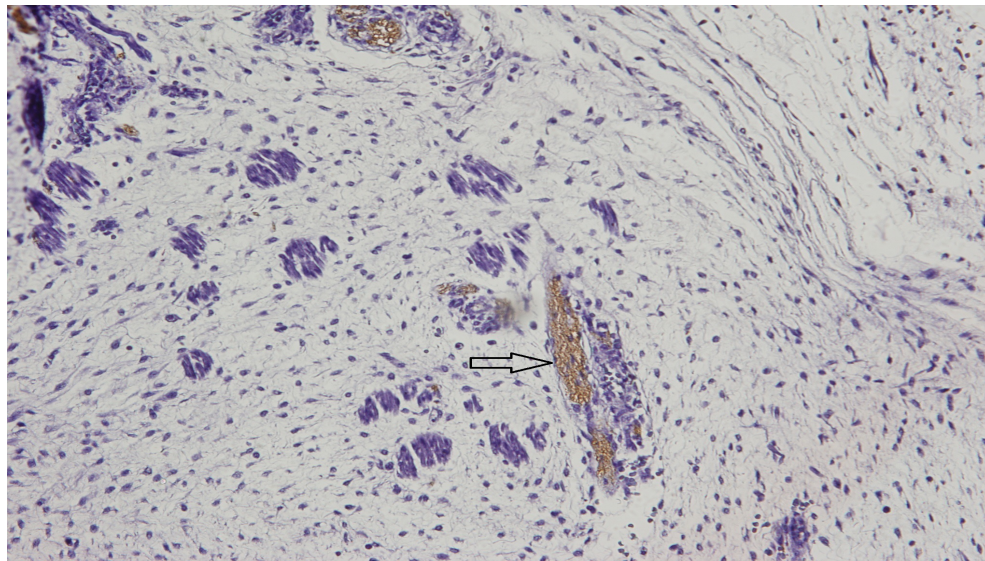


Control – 35WPC

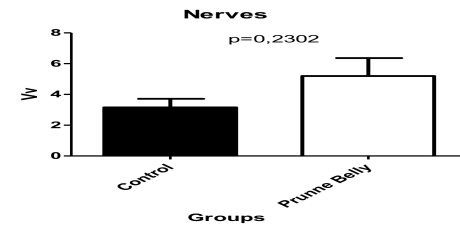


PBS – 31 WPC

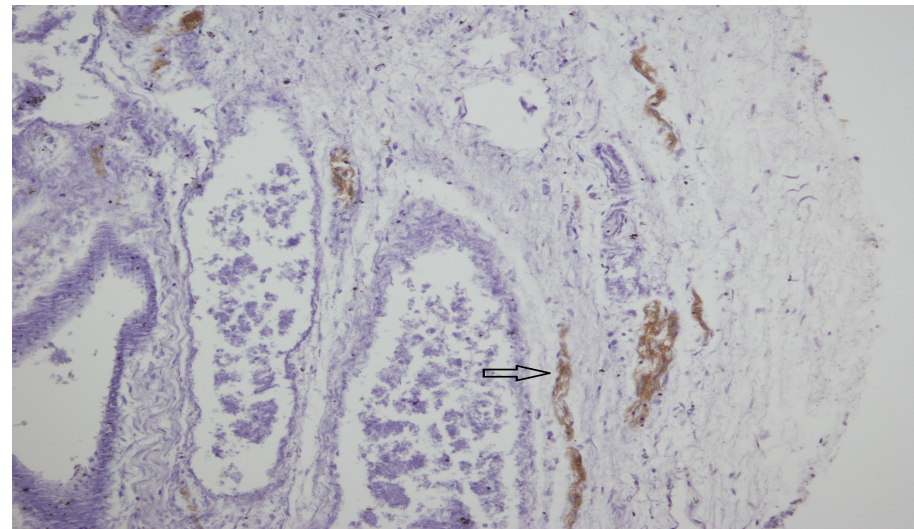
NERVS



PBS- 35WPC



Control – 31WPC



Conclusions

- » The gubernaculum of fetuses with PBS showed altered concentrations of collagen (predominance of collagen type III) and elastic fibers. These structural alterations could be factors involved in cryptorchidism in PBS.

Structural Study of Gubernaculum Testis in Fetuses with Prune Belly Syndrome

Suelen F. Costa, Waldemar S. Costa, Francisco J. B. Sampaio and Luciano A. Favorito*

From the Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil

Purpose: We compared and contrasted the structure of the gubernaculum testis in fetuses with prune belly syndrome and normal controls.

Materials and Methods: We studied a total of 6 gubernacula from 3 male fetuses with prune belly syndrome and a total of 14 from 7 male fetuses without an anomaly. Gubernacular specimens were cut into 5 μm sections and stained with Masson trichrome to quantify connective tissue and smooth muscle cells, with Weigert stain to observe elastic fibers and with picrosirius red with polarization to observe collagen. Immunohistochemical analysis was done with tubulin to observe the nerves. Images were captured with a BX51 microscope and DP70 camera (Olympus®). Stereological analysis was done with Image-Pro and ImageJ (MediaCybernetics®) using a grid to determine volumetric density.

Abbreviations and Acronyms

CGRP = calcitonin gene-related peptide

PBS = prune belly syndrome

Vv = volumetric density

WPC = weeks of gestation

Accepted for publication June 30, 2014.

Study received approval from the institutional ethical committee for human experimentation.

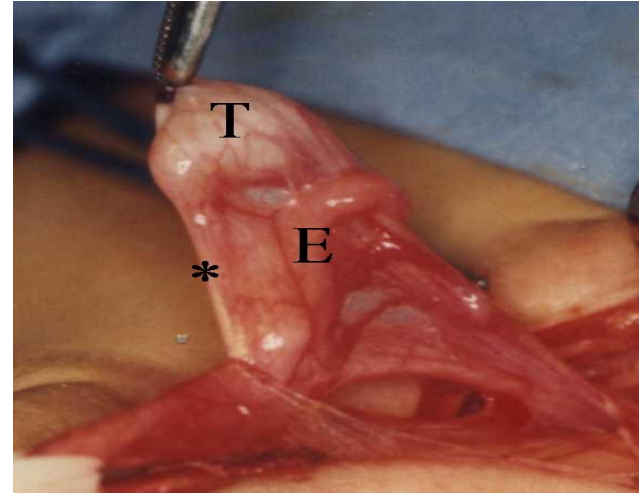
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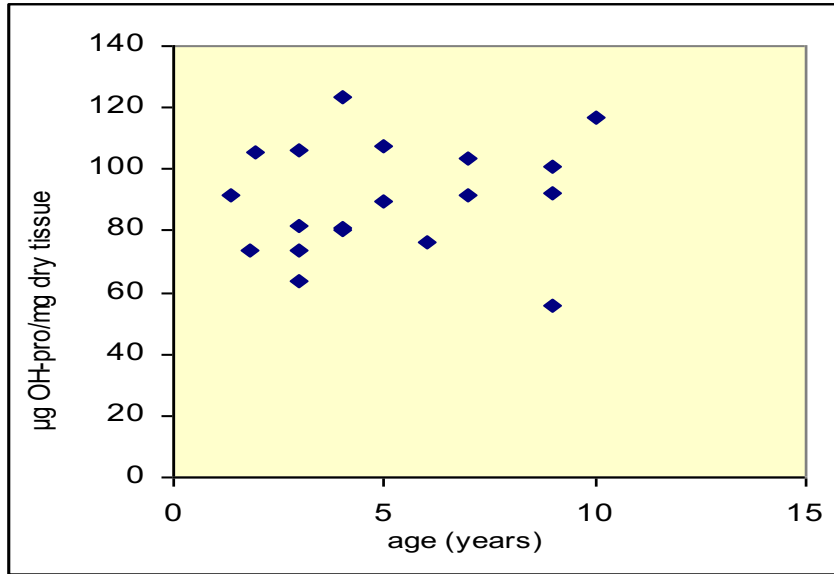
American
Urological
Association

GUBERNACULUM IN BOYS WITH CRYPTORCHIDISM



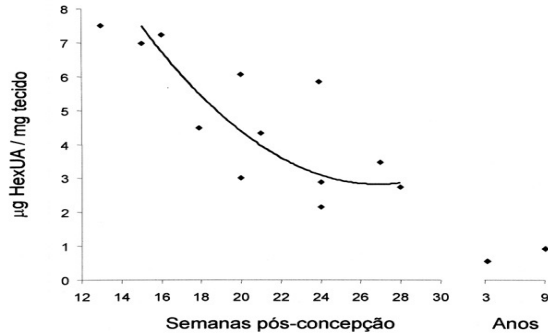
- » Essentially a fibrous structure
- » Increases collagen and Elastic Fibers

COLLAGEN – BIOCHEMICAL STUDY



- In the surgical samples, collagen concentration varied from 80-120µg/mg
- Concentrations were not correlated with patient age
- Collagen concentration was lower when the testis was located more proximally.

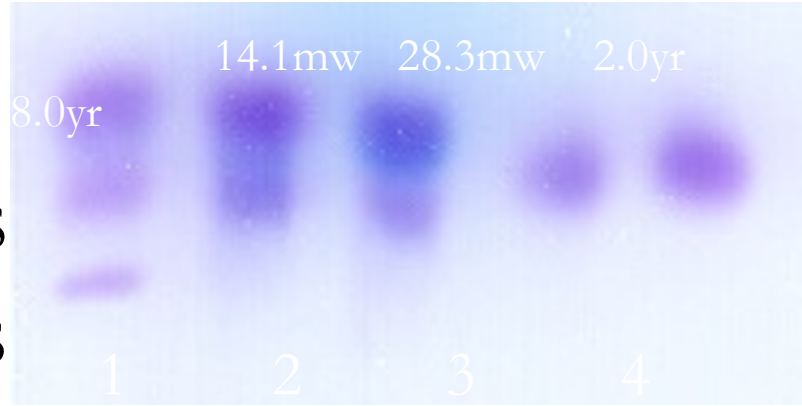
GAGS in GUBERNACULUM



CS 8.0yr

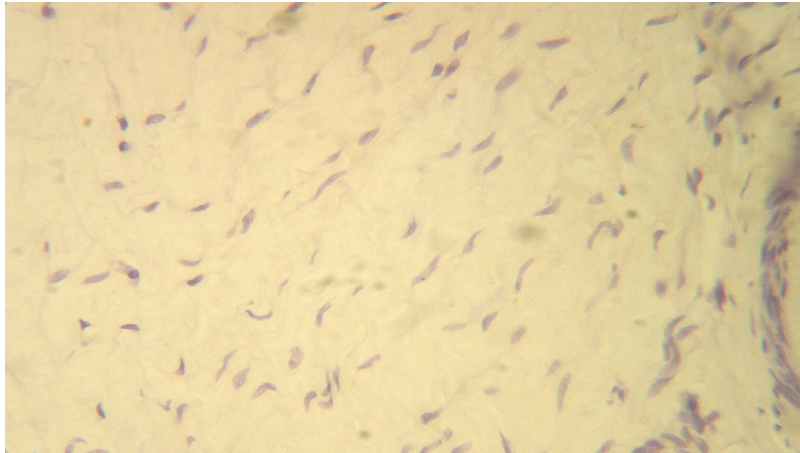
DS

HS



- » Early phases – Hydrated structure
- » Decreases of GAG with fetal age
- » At 16 WPC sulfated GAG - 55% chondroitin sulfate and 45% dermatan sulfate, and by the 28th SPC, 30 and 70% respectively
- » Gubernaculum from cryptorchidic children contained only dermatam sulfat.

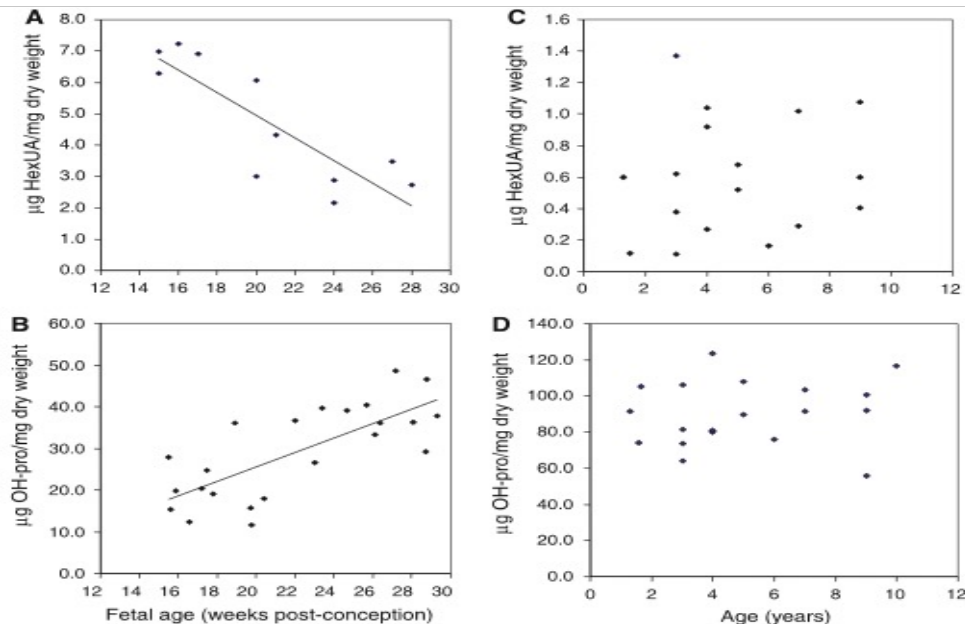
COLLAGEN – HISTOCHEMICAL STUDY



- Indeed, a lower collagen concentration when the cryptorchidic testis is more abdominal suggests that an underactivity of the factors that mediate this remodeling is associated with failure to migrate.

Extracellular matrix remodeling in the human gubernaculum during fetal testicular descent and in cryptorchidic children

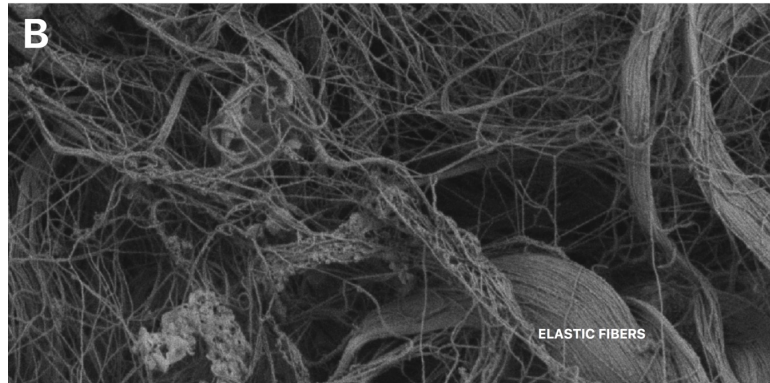
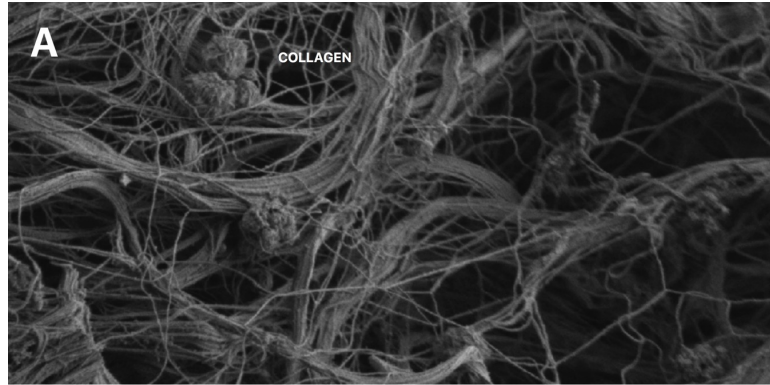
Isabel C. S. Soito · Luciano A. Favorito ·
Waldemar S. Costa · Francisco J. B. Sampaio ·
Luiz E. M. Cardoso



ULTRASTRUCTURAL ANALYSIS OF THE GUBERNACULUM IN UNDESCENDED TESTIS

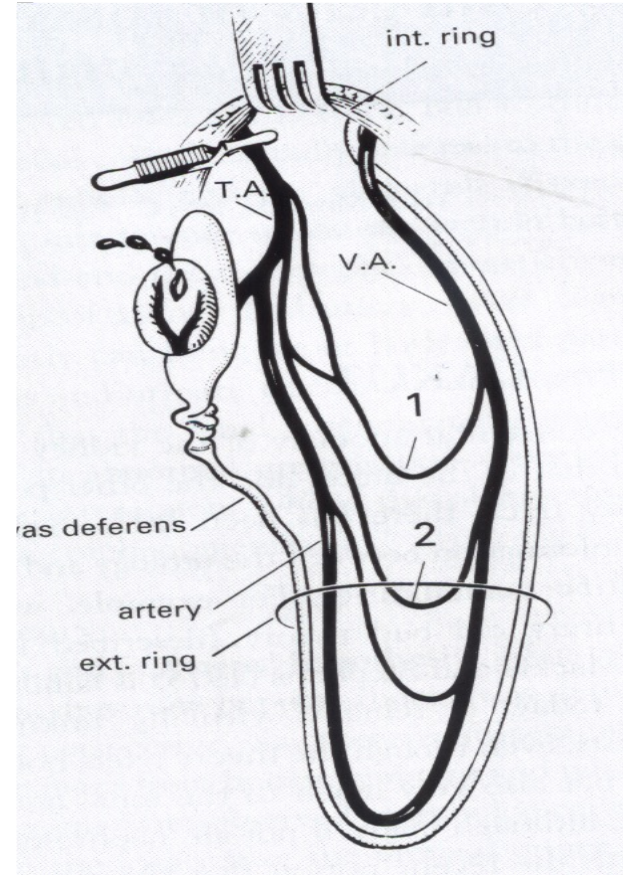
Gubernaculum is mostly collagenous in composition (collagen system fibers ranged in thickness from 0.2 to 0.4 μ m) with a clear disarrangement

Elastic fibers had the same thickness and were located mainly at the distal end of the gubernaculum



ARTERIAL SUPPLY OF THE HUMAN FETAL TESTIS

- » Preservation of an adequate arterial supply for the testis is crucial for successful orchiopexy.
- » We analyzed the number and origin of arteries supplying the fetal testis during its migration from the abdomen to the scrotum

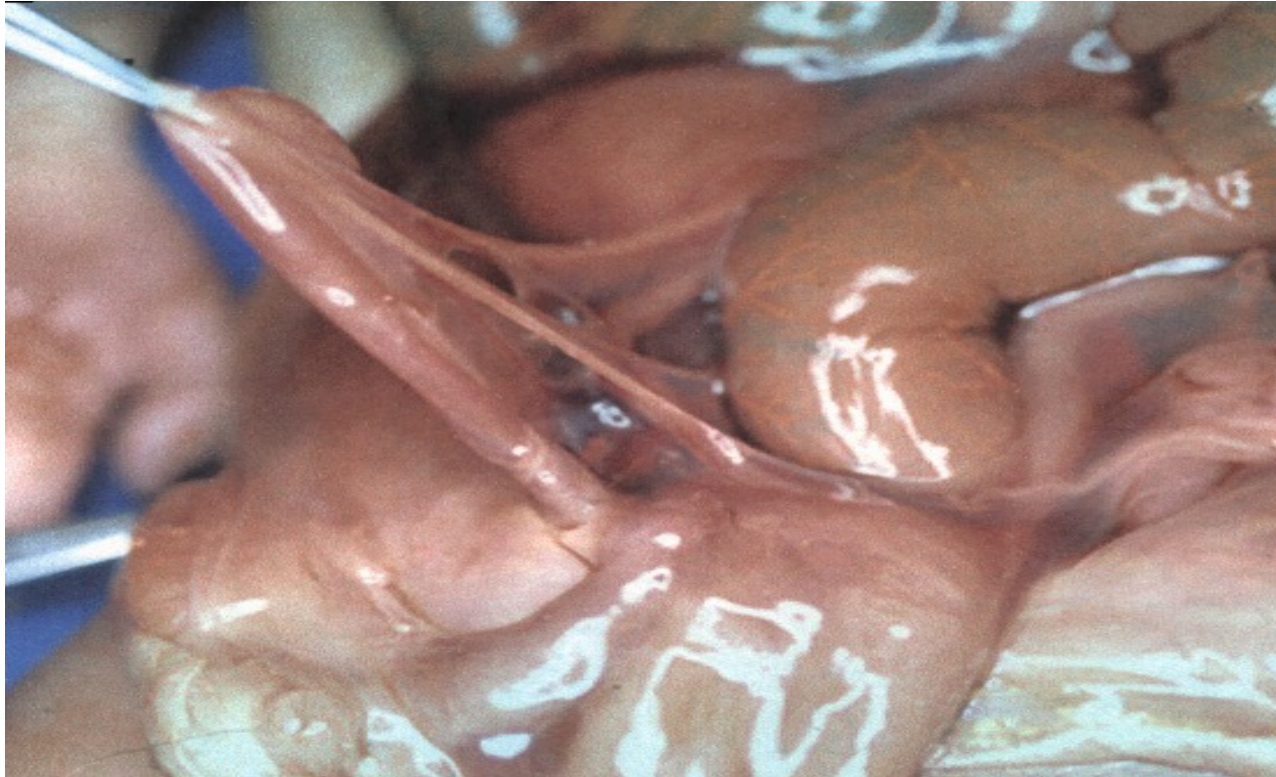


METODOS

- » **32 Human fetuses (13 to 22 WPC)**
- » **Injection of Microvascular silicone rubber resin to fill arterial tree**
- » **Scrotal – 5**
- » **Inguinal – 2**
- » **Abdominal - 25**



DISSECTION



ARTERIAL SUPPLY OF THE HUMAN FETAL TESTIS DURING ITS MIGRATION

FRANCISCO J. B. SAMPAIO,* LUCIANO A. FAVORITO, MARCELO A. FREITAS, RONALDO DAMIÃO
 AND EDUARDO GOUVEIA

From the Urogenital Research Unit and Division of Urology, State University of Rio de Janeiro, Rio de Janeiro, Brazil

ABSTRACT

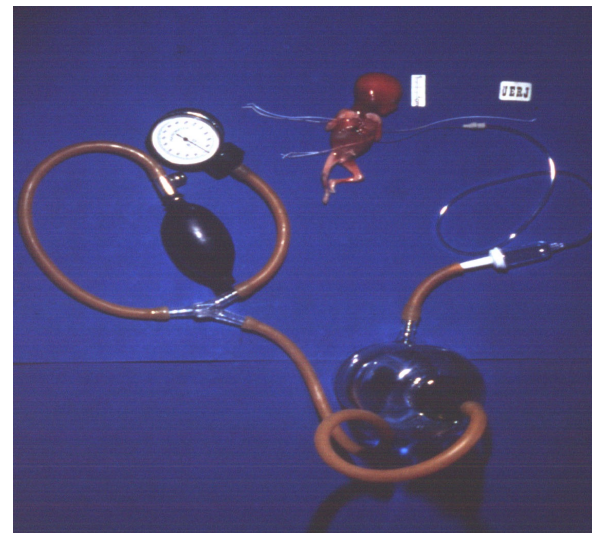
Purpose: Irrespective of the surgical technique chosen to treat high undescended testis, preservation of an adequate arterial supply for the testis is crucial for successful orchiopexy with maintenance of normal testicular size and texture. To provide an anatomical background for such a procedure, we performed a systematic study on the number and origin of arteries supplying the fetal testis during its migration from the abdomen to the scrotum.

Materials and Methods: We studied bilaterally 64 testes from 32 fresh human fetuses 13 to 33 weeks after conception. The fetuses were injected through the thoracic aorta with a microvascular silicone rubber red resin to fill in the arterial tree, thereby enabling identification and dissection of all arteries supplying the testes.

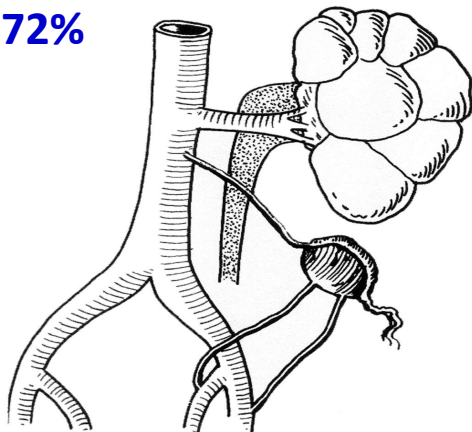
Results: Of the 64 testes 3 arteries (testicular, deferential and cremasteric) were found in 46 (71.9%), 2 (testicular and deferential) in 15 (23.4%) and 4 in 3 (4.7%).

Conclusions: The fetal testis is always supplied by at least 2 arteries (testicular and deferential arteries) and by 3 or 4 arteries in nearly 80% of the cases.

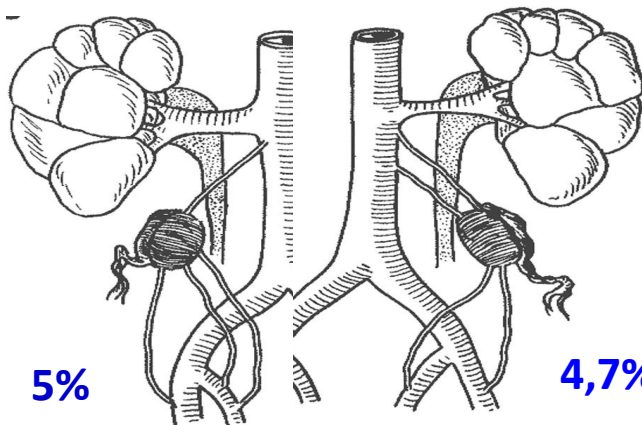
KEY WORDS: testis, arteries, fetal development, cryptorchidism, anatomy



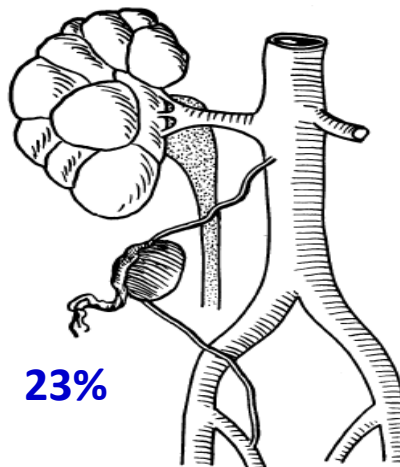
72%



5%



4,7%



23%

CONCLUSIONS

- » The fetal testis, much like what occurs in the adult, has a multiple arterial supply.
- » In all cases the deferential and testicular arteries were present
- » Surgical procedures involving division of the testicular artery early in life have a sound anatomical basis

Translational Research in Pediatric Urology

Basic and Clinical Aspects

Luciano Alves Favorito

Editor

 Springer

THANK YOU

