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Development of the human foreskin during the fetal period

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Summary. Aims: Foreskin development begins at twelfth gestational week through a circular invagination of the ectoderm in the glandular periphery that grows ventrally and totally involves the glans around the twentieth gestational week. Studies of foreskin formation chronology and its histological constituents in human fetuses are rare. The objective of this study is to analyze foreskin development during the second trimester of the human fetal period.

Methods: We studied twelve well-preserved human fetuses between thirteen and nineteen weeks post conception (WPC), according to the foot length criterion. The fetuses' weight ranged from 70 to 340 g and the crown-rump length from 11 to 18.5 cm. Their penises were formalin-fixed, paraffin-embedded and cut into 5 micrometers sections. Hematoxylin and eosin, Van Gieson solution, Gomori trichrome and Weigert staining were used.

Results: The glans was partially covered by the foreskin in the fetus at 13 WPC and almost completely covered by the foreskin in fetuses at 16 WPC and 17 WPC. The complete foreskin was formed only in the fetuses at 18 and 19 WPC, in which the foreskin totally covered the glans. In all the fetuses studied we observed the presence of preputial lamella and a large amount of mesenchymal tissue between the foreskin and glans.

Conclusion: The chronology of foreskin formation in the second gestational trimester is well documented in our article. It is a fast process that lasts around five weeks and is coordinated with penile urethra formation.

Key words: Foreskin, Penile embryology, Urethra, Human fetuses

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Introduction

The foreskin is a specialized mucocutaneous tissue that covers the glans of the penis. The foreskin function is to protect the glans from the irritant effects of urine and feces (Cold and Taylor, 1999). The foreskin is formed from a combination of the ectoderm, neuroectoderm and mesenchyme. The formation results in a pentalaminar structure that is a combination of the following layers: Mucosa (squamous epithelium), lamina propria, dartos muscle, dermis and glabrous outer epithelium (Cold and Taylor, 1999).

Foreskin development occurs at the end of the third gestational month and is completed by the fifth gestational month, around the eighteenth week post-conception (Baskin, 2000; Van der Werff et al., 2000; Baskin, 2007). Prepuce formation is directly related to the formation of the glans and penile urethra (Altemus and Hutchins, 1991).

There are several studies in the literature about formation of the penile urethra in humans (Altemus and Hutchins, 1991; Kurzrock et al., 1999, 2000; Penington and Hutson, 2002). Nevertheless, specific studies about the foreskin in human fetuses are rare (Glenister, 1954).

The main objective of this work is to study the chronology of foreskin formation in human fetuses, by evaluating foreskin structure during the human fetal period and its relationship with the penile urethra and the penile glans.

Materials and methods

We studied 12 penises obtained from 12 fresh human fetuses between thirteen and nineteen weeks post conception (WPC). The fetuses were macroscopically well preserved and no signs of congenital malformation were detected. The gestational age was determined in WPC, according to the foot-length criterion. This criterion is currently considered to be the most

acceptable parameter to calculate gestational age (Hern, 1984; Mercer et al., 1987; Platt et al., 1988; Costa et al., 2002; Favorito et al., 2004). The fetuses were also evaluated regarding crown-rump length and body weight immediately before dissection. All measurements were taken by the same observer. The fetuses weighed between 70 and 310 grams and the crown-rump length was between 11 and 18.5 cm (Table 1).

After dissection, each penis was carefully removed with the aid of a stereoscopic lens with 2.5x magnification, cross-sectioned at its base and immersed in Bouin's solution for 48 to 72 hours. The specimens were then processed by routine methods, and embedded in paraffin, from which 5μm thick sections were obtained.

In four fetal penises we performed longitudinal midline cuts and in eight fetal penises we performed transverse cuts. The transverse sections were made in four regions: a) the penis body; b) the coronal sulcus; c) the central portion of the glans and d) the distal portion of the glans.

For histological analysis the penis sections were stained with Hematoxylin and eosin to verify the integrity of the specimens; Van Gieson' solution and Masson's trichrome for collagen evaluation; and by the Weigert's Resorcin-fucsin technique, with oxidation in 10% ozone to analyze the elastic fibers.

The present study was approved by our institution's bioethics committee.

Table 1. The table shows the fetal parameters and the gestational age of the 12 fetuses.

FETUS	AGE (WPC)	WEIGHT(G)	CRL (cm)	TL (cm)
1	13	70	11	16.5
2	14	120	13	18.5
3	16	195	14.5	21
4	16	190	14	20.5
5	16	210	15	22.5
6	16	210	15.5	23
7	17	265	16.5	23.5
8	17	285	17.5	24.5
9	18	310	17.5	25
10	18	325	18.5	27
11	18	340	18.5	28
12	19	310	18	27

CRL: crown-rump length; TL: Total length of the fetus; cm: centimeters; G: grams.

Results

Table 2 and figure 1 show the chronology of the preputial formation during the second gestational

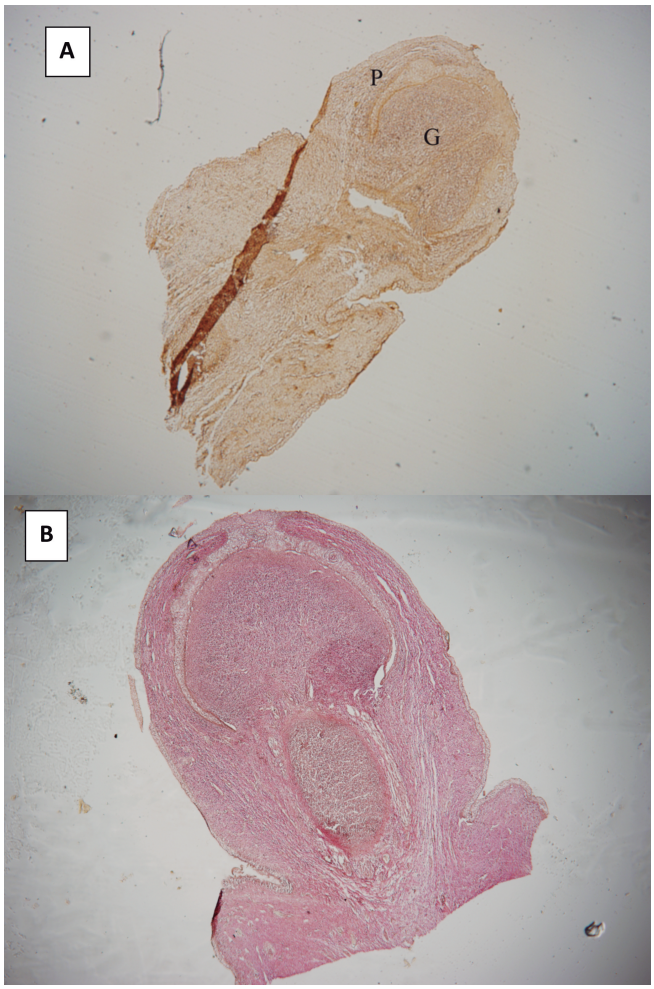

Fig. 1. Chronology of foreskin formation: **A.** Photomicrograph of a 13 WPC fetal penis. The foreskin covers the central portion of the glans (arrows). Van Gieson 40X. **B.** Photomicrograph of a 16 WPC fetal penis. The foreskin covers almost the entire glans (arrows) except for its distal extremity. Van Gieson 40X. G, glans; P, prepuce.

Table 2. The table shows the developmental steps of the foreskin, frenulum, preputial lamella and glandular urethra in fetuses during the 13th to 19th weeks post conception (WPC).

AGE	FORESKIN	FRENULLUM	LAMELLA	GLANDULAR URETHRA
13-14 WPC	Covers central portion of glans	Has not begun to form	Large amount	Is forming
15-17 WPC	Covers most of glans	Is forming	Large amount	Is forming
18-19 WPC	Covers all of lamella	Formation complete	Small amount	Formation complete

trimester.

We observed in Figure 2 the development of the preputial frenulum. At 16 WPC, the preputial frenulum is not totally formed (Fig. 2A,B), but at 18 WPC the frenulum is fully developed and fixed in the ventral portion of the glans (Fig. 2C,D).

Figure 3 showed the characteristics of the preputial lamella during the second gestational trimester. We observed in Fig. 4 the chronology of the preputial formation during the second gestational trimester.

Discussion

The foreskin starts to develop around the twelfth WPC as an epithelial fold that grows dorsally beside the penile body, covering the coronal region of the glans (Baskin, 2000). The foreskin does not cover the glans in the first gestational trimester, due to the fact that the glandular urethra is not formed until then.

The frenulum of the foreskin is composed of mesenchymal tissue covered by an epithelium that unites

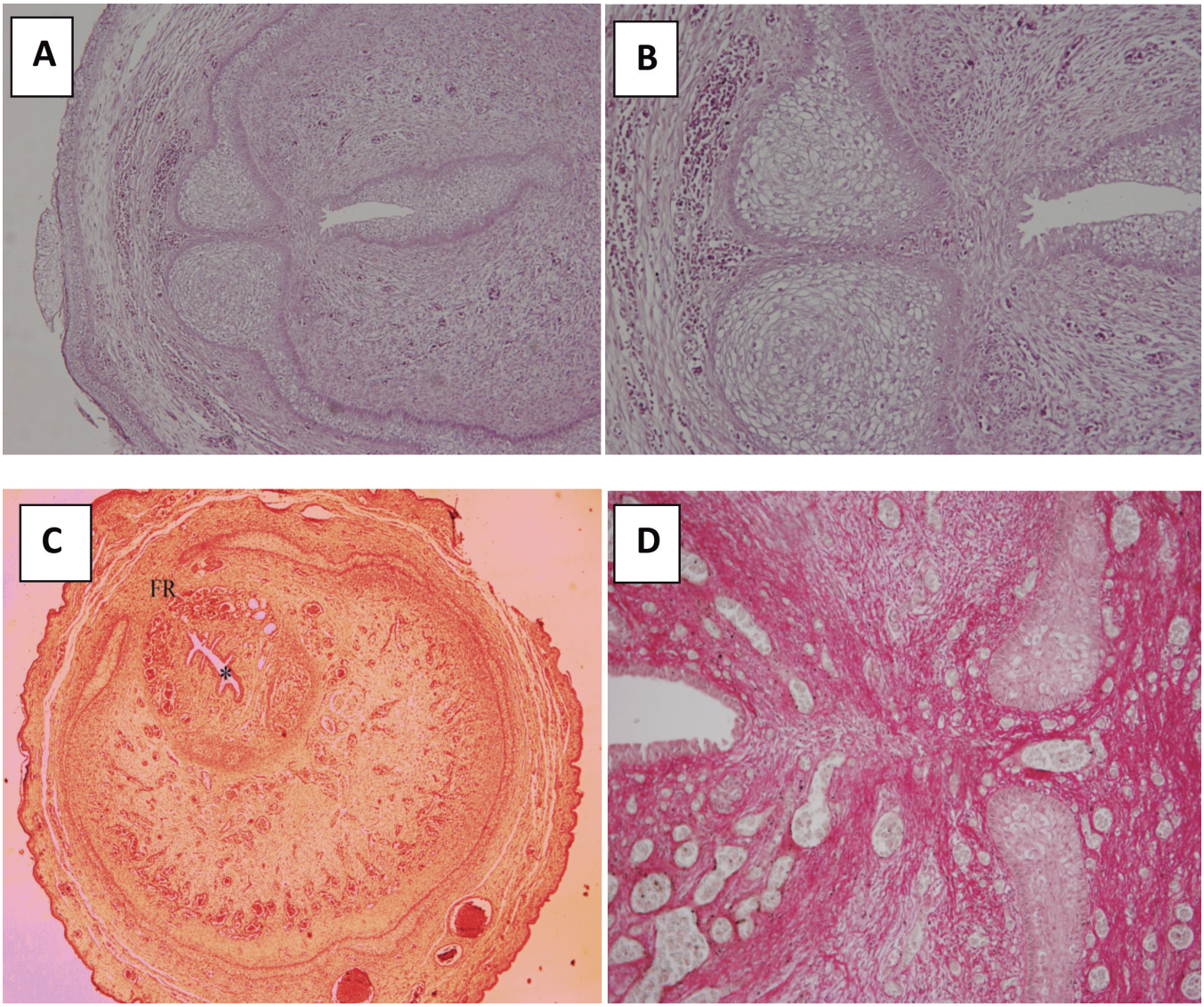

Fig. 2. Preputial frenulum formation. **A.** Photomicrograph of a 16 WPC fetal penis showing the urethral plate and the glandular urethra in formation (*). The preputial frenulum has not completed its development. Hematoxylin and eosin. **B.** Photomicrograph of the same fetal penis of figure 2A, stained by hematoxylin and eosin. **C.** Photomicrograph of a 18 WPC fetal penis showing that the frenulum and penile urethra are fully formed. Van Gieson. **D.** Photomicrograph of a 18 WPC fetal penis, showing the preputial frenulum fixed to the glans. Van Gieson. FR, frenulum, *, penile urethra, UP, urethral plate, L, lamella and G, glans. A, x 100; B, D, x 200; C, x 40

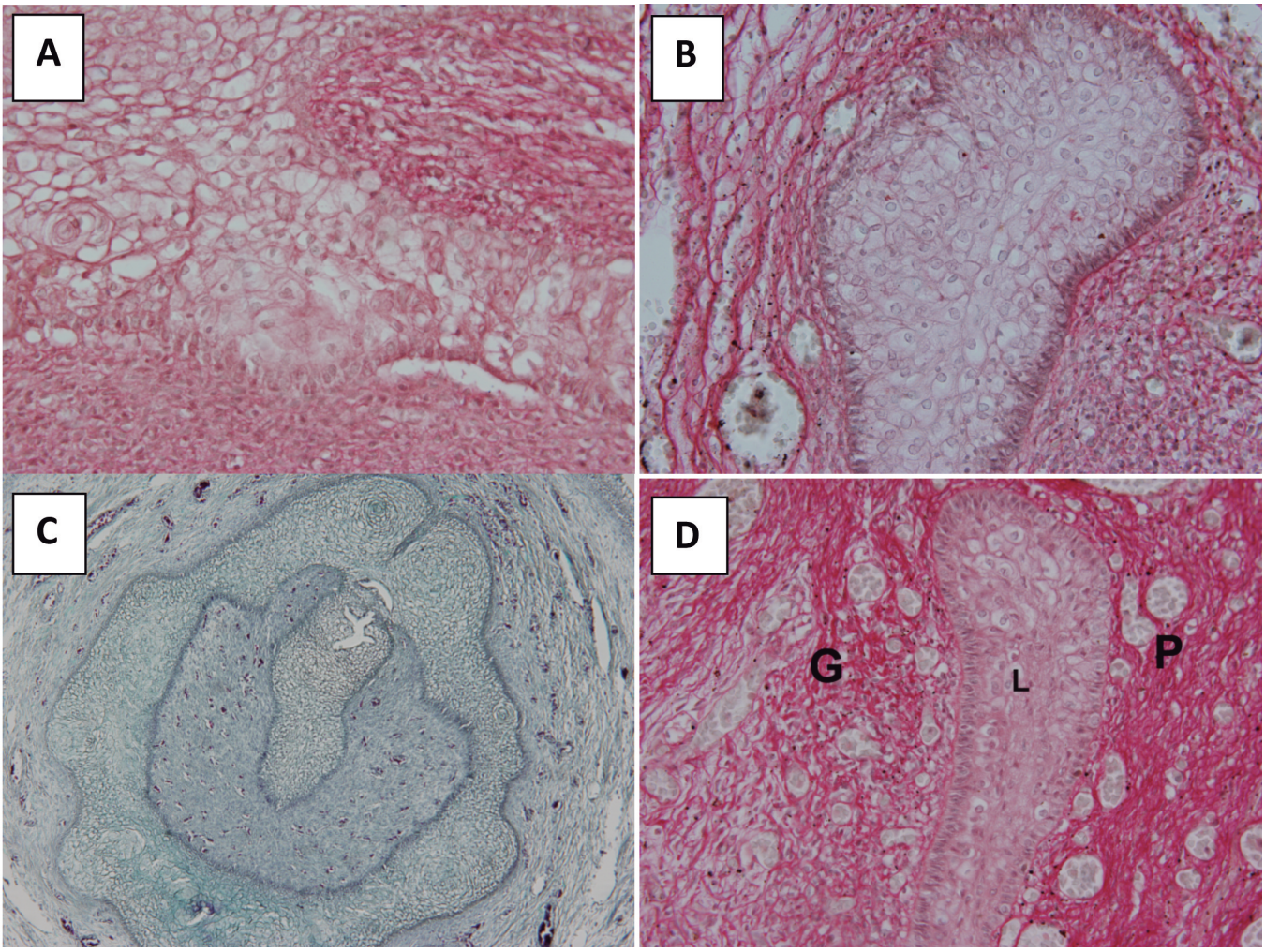

Fig. 3. Characteristics of the Preputial lamella. **A.** Photomicrograph of a 13 WPC fetal penis showing a large amount of mesenchymal tissue (lamella) which fills the space between the prepuce (P) and the penis glans. Hematoxylin and eosin. **B.** Photomicrograph of a 16 WPC fetal penis showing a large amount of preputial lamella. Van Gieson. **C.** Photomicrograph of a 16WPC fetal penis, showing a large amount of mesenchymal tissue. The preputial lamella joins the urethral plate. At this point of penile urethral formation, the urethral plate is invaded by the mesenchyme of the preputial space, canalizing and uniting itself to the penile urethra. Masson trichrome. **D.** Photomicrograph of a 18 WPC fetal penis showing a smaller amount of preputial lamella. Van Gieson. P, prepuce*, glandular Urethra, G, glans, L, lamella. A, B, D, x 400; C, x 100

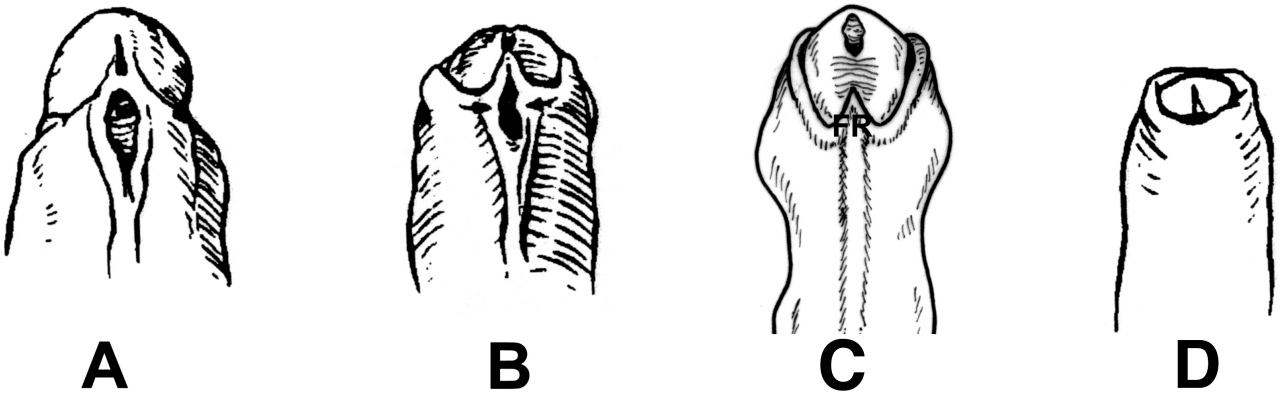

Fig. 4. Chronology of fetal foreskin formation, based on the Stephens Scheme (Stephens et al., 2002). **A.** Schematic drawing of a fetal penis with thirteenth WPC, showing the foreskin already covering a part of the glans. Arrows show the closing of the penile urethra. **B.** Fetal penis with 16 WPC showing the partially formed foreskin frenulum (Fr) and; **C.** Fetal penis at 19 WPC with a complete foreskin that covers the entire glans.

the prepuce to the ventral region of the glans (Sommer and Stephens, 1980; Altemus and Hutchins, 1991; Baskin, 2000). The frenulum is formed by the midline union of the frenulopreputial fold. The preputial region of the frenulum divides the glandular urethra into two segments: the proximal, which derives from the penile urethra, and the distal, whose origin is controversial. We observed that the preputial frenulum was not totally formed in the 16 WPC fetuses, but was fully formed and fixed at the ventral region of the glans in the 18 WPC fetuses. At that time the proximal penile urethra was also fully developed.

The preputial lamella is a structure actively involved in the formation of the foreskin, glans and urethra (Altemus and Hutchins, 1991; Baskin, 2000; Grumbach and Conte, 2003). It is formed by mesenchyme which fills the space between the glans and the foreskin and, during development, extends up to the urethral plate. Glenister (1956) in his work suggested that the foreskin rolls over the base of the glans, leaving a groove between it and the coronal sulcus. This groove is filled simultaneously with actively proliferating glanular lamella. In our sample the preputial lamella was present in all fetal penises, but in larger amounts in the younger specimens (13 to 16 WPC), than in the older ones (18 and 19 WPC). Our findings demonstrated that older gestational fetuses had a smaller amount of mesenchyme in the preputial space. It is possible that continued reduction of preputial mesenchyme could lead to fusion of the prepuce and glans, thus explaining the fact that at birth the glans and foreskin are fused in the majority of cases, not allowing the exposure of the glans (Van der Werff, 2000; Wiswell, 2000).

At 16 WPC, a period in which the penile urethra is completing its formation (Stephens et al., 2002), the foreskin already extends itself to the distal portion of the glans. In this phase, the frenulum of the foreskin is not totally formed. The end of foreskin and frenulum formation occurs by the eighteenth gestational week. In fetuses with 18 to 19 WPC, the frenulum is fully formed and the foreskin covers the entire glans. The amount of mesenchymal tissue filling the preputial space tended to decline in the older gestational fetuses, leading to close proximity between the foreskin and glans in these older fetuses.

The chronology of foreskin formation in the second gestational trimester is well documented in our article. It is a fast process that lasts around five weeks and is coordinated with penile urethra formation. In summary, foreskin formation begins in the 12^{th}-13^{th} gestational weeks and is complete by the 18-19^{th} weeks post conception.

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