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CONTROVERSY ABOUT EMBRYOGENESIS AND ORGANISATION OF HUMAN FEMALE URETHRA: A REVIEW
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ABSTRACT

***Objective*: To assess current knowledge on development and associated structures.**
***Data sources*: Current scientific publications in the pubmed data base on the development of human female urethra were reviewed. The embryology of human female urethra and its associated structures is presented.**
***Study selection*: The following search words: urethra development, female urethra development, and male urethra development were used.**
***Data extraction*: The first 100 publications from urethra development search and thereafter 100 publications excluding those in the first search were reviewed to determine whether they described development of female urethra.**
***Data synthesis*: There are limited studies describing the formation of female urethra. Unlike male urethra, female urethra does not undergo masculinisation meaning there is no formation of clitoral urethra. Like the male urethra, there are female urethra associated glands whose presence and functions remain speculative. Female urethra associated structures including Skene's glands also referred to as female prostate, corpus spongiosum of female urethra and what has been described as the G-Spot may all be congenital malformations considering that they are not uniformly present.**
***Conclusions*: Female urethra development differs from that of males though there are some similarities. Studies to elucidate the development of female urethra are needed to clarify some of the misconceptions and to provide embryological explanation of gross and histological features of female urethra.**

INTRODUCTION

The urethra has both reproductive and urinary functions in males while in females, it has only urinary function. Despite many studies examining development of the urethra and associated congenital malformation, there are several unclarified questions, in particular related to female urethra. There are anatomical and developmental differences between male and female urethra. In particular, the penile part of male urethra has corpus spongiosum which is considered to be lacking in female urethra, though there are some authors belief it exists (1.2). Female urethra does have para-urethral glands also called Skene's glands (3) which are considered to be the homologous of male prostate gland (4-6). Female urethra and associated glands has been subject of intense interest in relation to female sexuality and their potential role or function. There have been suggestions that the female urethra and structures related to it might constitute an erotic zone or tissue often referred to as the G-Spot (7-11).

The female urethra and its associated structures are considered to play a significant role in sexual response in females (7-10). Some studies have documented presence of the G-Spot (7-10) while other have not been able to find it (1,12). Others have described the phenomenon of female ejaculation (13) while others consider it does not exist (1,14,15) or it is not even part of the female sexual response (14). Occurrence of female ejaculation is associated with presence of Skene's glands or some coital urethral incompetence resulting in female squirting (16). Skene's gland have been described as a group of glands arranged in long ductal structures situated in the caudal two thirds of the urethra (4,6). They are not universally found in all women (4,5). They contain prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) on immunostaining (4-6).

The presence or absence of female urethra associated structures and their functions remain speculative. The constitution of glands surrounding the human female urethra has been under debate; especially regarding as to what extent they equal the male prostate. It is not certain whether females have corpus spongiosum and if it is present, what is its function? Since Skene's glands are not universally found in all women, are they vestigial developmental remnants and if present, do they have an important function? Without a clear anatomical basis or explanation of the female urethra associated structures, there is a lot of suppositions and ignorance. This review on development of female urethra was undertaken to clarify whether there is embryological explanation of the supposed female urethra associated structures.

MATERIALS AND METHODS

The electronic pubmed data base was searched for papers published by end of July 2014, using the search words: urethra development, female urethra development, and male urethra development. The first 100 publications from urethra development search and thereafter 100 publications excluding those in the first search, abstracts where available were reviewed to determine whether they described development of female urethra. None of the 300 publications reviewed specifically had a title on development of female urethra and none of the publications objective was to describe development of female urethra. Other publications going back to 1954 which were considered appropriate were also reviewed. Relevant publications with description of male and female urethra development are summarized below to form the basis of discussion of development of female urethra and associated structures.

RESULTS

Common development of the urethra in males and females: The urethra arises from endoderm which gives rise to epithelium, and splanchnic mesenchyme which forms the surrounding soft tissues. The urinary bladder and urethra arise from the endodermal urogenital sinus after the urorectal septum (i.e., Tourneux's fold) partitions the embryonic cloaca into the ventral urogenital sinus and the dorsal rectum (17,18). At around five weeks of human gestation and at E11–12 in mouse, the urogenital sinus is further separated into the anterior vesicourethral canal and the posterior urogenital sinus. The anterior portion of the urogenital sinus (i.e., anterior vesicourethral canal) becomes the bladder, which is connected to the allantois during early fetal life. The posterior portion of the urogenital sinus later develops into the phallic urethra (also called spongy or penile urethra) in the male and the lower portion of the vagina and vaginal vestibule with perineal urethra orifice in the female (19,20). Male urethra is divided into three segments: pre-prostatic, prostatic, and membranous urethra. It is not certain whether female urethra corresponds to the male pre-prostatic, prostatic, and membranous urethra since the histochemical study by Hadid *et al.*, (21) suggests there may be no membranous urethra in human females.

The animal model of male urethra development: Since there only a handful of studies describing female urethra development, development of male urethra is described to contextualise development of female urethra. Development of the genital tubercle is indistinguishable in male and female embryos (ambisexual stage) until approximately E16, when the urethral plate begins to be masculinized to form the penile urethra, marking the beginning of the hormonally controlled period of sexual differentiation (22). The genital tubercle is composed of mesoderm, surface ectoderm and cloacal endoderm that extends into the tubercle to form the urethral plate epithelium.

The origin, extent and topographical relationships of the urethral plate has been a subject of debate (22-25). Current consensus is that the urethral plate epithelium gives rise to the entire penile urethra (18,2,22) though the longstanding view has been that the distal / glandar urethra arises from an invagination of distal ectoderm (19,26), thereby giving it a dual origin.

The urethral plate is described as extending along the entire length of the genital tubercle shaft in mice (24,27,28). In the rat, Kluth *et al.*, (29) found no evidence of a urethral plate and described the phallic cloaca as extending as far as the tip of the genital tubercle whilst Forsberg (23) considered the urethral plate to be confined to the glans. In the mouse model, Hynes and Fraher (24,27,28) described phallic cloaca as extending to two thirds of the glans. In marsupials at birth, the urethral plate extends to the tip of the genital tubercle and reaches the rostral surface of the glans (30). These animal models show variability in development of male urethra in different species.

Seifert *et al.*, (31) described three phases of urogenital development in mice. Phase one also called initiation phase is independent of sonic hedgehog (Shh) influence while phase 2 or the anogenital phase in which there is continued septation of the cloaca and outgrowth of the genital tubercle is facilitated by Shh. At the end of the anogenital phase, embryos have developed separate anorectal and urogenital sinuses, and the genital tubercle is separated from the anus by the perineum (31). The last phase is external genital phase in which definitive external genitalia is formed. This phase is also influenced by Shh. Seifert et al., (31) showed that disruption of Shh activity during either of these phases produces similar defects in male and female mice, indicating that Shh is required throughout the sexually indifferent period of anogenital development.

The human model for male urethra development: Description of development of the male urethra is variable without a common agreed process. For example, Glenister (26) described the urethral plate as extending along the entire length of the genital tubercle (except for the distal one third of the glans) but Altemus and Hutchins (32) considered it to be confined to the glans in humans. According to Glenister (26), the extent of the urethral plate depends on the stage of development of the urethra. Study of human fetus found that male urethra development does not include ectodermal ingrowth (21).

The human model of female urethra development: The developed female urethra is about 4-cm tubular structure that begins at the bladder neck and terminates at the vaginal vestibule. Female and male urethra share similar development in terms of common origin from the urogenital sinus which is formed from the cloaca after formation of urorectal septum (17-20). Krishnan et al., (33) study showed that the prostatic urethra and membranous urethra are derived from the urogenital sinus. Given that the same urogenital sinus forms the female urethra, Krishnan *et al.,* (33) considered this stage to be independent of androgens.

From the developing male and female urethra, there are glands which form as out pocketing from the duct (18,20,33) including male prostate and paraurethral glands. Female urethra is considered to be the equivalent of male prostatic and membranous urethra. Despite this similarity, female urethra does not develop posterior urethral valves (20) unlike in males. The female urethra develops from the urogenital sinus endoderm and the surrounding splanchnic mesoderm (18,19). Glenister (26) studying human material described the formation of urethral groove in female foetuses which was identical to that formed in male foetuses. Through microscopic examination, Glenister (26) showed that though to the naked eye, the urethral groove appeared to stop short of the coronary sulcus, it did in fact extend on to the under-surface of the glans in two foetuses examined. From the observation by Glenister (26), it appears that as female foetus progressively grow, the urethral plate degenerates (retrogression) from the genital tubercle and clitoral phallus such that by 100mm phallus stage, the urethral plate could not be identified. Similar observations were reported by Penington and Hutson (34).

Female corpus spongiosum: According to Puppo (1) review and Van Turnhout *et al*., (2), the corpus spongiosum of the urethra is present in all women, as in the male. It is described as cavernous tissue rich in veins, situated at submucosal level and among the muscular bundles of the smooth muscular tunica of the urethral wall. Thus according to Puppo (1) and Van Turnhout *et al*., (2), erectile structures are the same in females and in males. The affirmative presence of female corpus spongiosum by Puppo (1) is not confirmed by other studies (35,36). Hinata et al., (36) study on detailed histological investigation of human female urethra showed abundant veins surrounding the middle urethra. According to Ginger and Yang (35) histological study of female sex organs, the clitoral bulbs which are erectile are found in the anterior aspect of the distal urethra and do not encircle the urethra nor the introitus. Up to 3 cm from the urethral meatus, the urethra is surrounded by non-erectile vascular tissue (35).

Female prostate: Ginger and Yang (35) study using cadaveric materials documented female para-urethral glands which were isolated and not organised like the male prostate. Cohen *et al*., (37) using cystoscopic male urethral biopsies found small glands along the male urethra which were PSA expressing. Cohen et al., (37) proposed that these small male para-urethral glands be referred to as "minor prostatic glands" in contrast to the existence of a finite prostate gland. Could the minor prostatic glands proposed by Cohen *et al*., (37) be equivalent to the Skene's glands in females?

DISCUSSION

Development of female urethra is less well investigated as compared to male urethra. There are no specific animal or human studies which have investigated development of female urethra, though, when urethral developmental defects occur in females, they tend to be more severe than in males (17). Despite the similarities with male urethra, there are significant developmental and anatomical differences. Notable is the finding that in human, at indifferent external genitalia stage, urethral plate extends all the way to the tip of developing phallus, with retrogression in later stages in females while in males, there is no retrogression of the urethral plate. As noted above, male and female urethra developmental processes are similar in animal and humans with subtle differences in the process between different animals and humans.

The apparent differences could however represent real developmental differences between species based on different developmental stages being reported. Study by Glenister (26) reported presence or absence of urethral plate in developing females depending on stage of development. A female foetus with phallus of 100 mm, there was no urethral plate while at 80mm, the urethral plate was seen extending up to the clitoral glans (26). The differences could also be related to the mechanisms of urethral development. In urethral tubulogenesis, classical description is that urethra develops from in-situ migration of cells to form the urethral plate with subsequent formation of urethral tube. The male urethra forms by cavitation of the solid urethral plate with fusion of the tube in proximal-distal direction in males. The formation of pre-prostatic, prostatic and membranous parts which are similar in females is not well understood. Hynes and Fraher (24,27,28) proposed that except for the phallic part of male urethra, the rest of the urethra forms as a result of mesodermal compression which causes narrowing of urogenital sinus. The hypothesis of mesodermal compression could explain the differences seen in different species and human. The mesodermal compression could cease at different levels or stages of development in different species thereby explaining the anatomical observations that the urethral plate may or may not reach the tip of the phallic cloaca (22,24,26-28).The hypothesis of mesodermal compression is supported by the finding that persistence of the cloacal membrane which can cause posterior displacement of the mesoderm of the urogenital tubercle, results in division of the urethral plate (25). Indeed, persistence of cloaca membrane is associated with urethral duplication and bifid clitoris (25). The study by Seifert *et al*.,(22) using cell fate mapping showed expansion of the dorsal swelling and the urorectal septum mesoderm, on the dorsal and ventral sides of the urogenital sinus which was associated with a dorsoventral compression of the urogenital sinus. Thus morphogenesis of the cloacal mesoderm affects development of the genital tubercle.

In the process of masculinisation of the genital tubercle, there is arrest of further development of female genital tubercle while it continues in males (18,19). In males, there is formation of urethra and corpus spongiosum but not in females (20). Preputal folds form the labia minora in female and male urethra (18,19,38). The histological organisation of the labia minora is different from corpus spongiosum and is considered not to be classical erectile tissue (35). Ginger and Yang (35) study as well as the study by Ostrzenski (7,8) and Ostrzenski *et al*.,(9) do not support the assertion by Puppo (1) and findings by Van Turnhout *et al*.,(2) since none demonstrated erectile tissue in the relation to the urethra. Further, the presence of female corpus spongiosum is not supported by current studies describing development of female urethra (20,22,39).

If indeed there is true female urethra corpus spongiosum, this may be a developmental defect. There are case reports of urethra congenital malformations and histological studies which may lend support to the preposition that developmental defect may account for the presence of corpus spongiosum and glands associated with the female urethra (3,40). Mahalik *et al.*, (40) reported male like-penis in female with a normal vagina. Dwyer (3) study found presence of Skene's gland in only 33% of the cadavers examined while Thabet (10) study found histological G-spot containing epithelial, glandular and erectile tissue-like structure in 47.4% of all cases. Dietrich *et al*., (4) reported presence of female prostate in 50% of the women examined. The formation of male-like penis may be explained by persistence of the urethral plate in a true female. Hadidi *et al*., (21) study reported differentiation of mesenchyme surrounding developing urethra into a vascular corpus spongiosum in human by 13th week. It is therefore assumed that persistence of urethral plate may be associated with development of corpus spongiosum. This seems to be the case since the case reported by Mahalik *et al*., (40) did have rudimentary corpus spongiosum of the urethra. From the foregoing, it is probable that various degrees of retained urethral plate in the anterior vaginal wall may explain the findings of erectile-like tissue covering lower female urethra which has been found in tissues reported by Thabet (10), or what Puppo (1) and Van Turnhout *et al.*, (2) calls corpus spongiosum of female urethra. Second, failure to demonstrate physical G-Spot (12,14,41,42) despite very intensive efforts may be accounted for by the proposal that the tissues found in the documented G-Spot to date are indeed congenital defects of the female urethra. The presence of corpus spongiosum, Skene's glands may be part of the spectrum of disorder of the female genital system of no functional significance, though they may cause clinical problems.

The counter argument for the presence of female urethra corpus spongiosum, is that it does not exist. Though there are physiological and physical changes which occur in sexual response, these changes may not be dependent on presence of corpus spongiosum of the urethra in females. The labia minora and majora do manifest physical changes in response to sexual stimulation, yet these tissues do not have the classical erectile tissue, rather they have spaces which are limited by connective tissue, not smooth muscles (35). From Ginger and Yang (35) study, there is no definitive corpus spongiosum surrounding the female urethra.

In conclusion, this review shows there is scant information on development of female urethra, yet there are many clinical entities which may be explained by better understanding of female urethra development. Important is the lack of any embryological description of structures which have been suggested to form the corpus spongiosum surrounding female urethra and the so called G-Spot. It is probable that the tissues seen or called G-Spot by those who support its existence may actually be congenital defects of development of female urethra while the failure to reproduce such results of the G-spot may also be due to the fact that these are not universal structures, if they are the result of congenital malformations. There is need to undertake more cell fate studies on development of female urethra to clarify its development.

CONFLICT OF INTEREST

No conflict of interest.

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