

# **Understanding the Functional Significance of the Labia Minora: A Scoping Review on Sexual Physiology**

## 1 **Introduction**

2 The labia minora, a vital yet understudied part of female genital anatomy, are two inner folds of skin that  
3 extend outward from the vaginal and urethral openings, encompassing the vestibule. Part of the  
4 ectodermal-derived vulva, the labia minora stretch from the clitoris obliquely downward, laterally, and  
5 backward on either side of the vulvar vestibule, terminating between the base of the vestibule and the  
6 labia majora<sup>1</sup>. The posterior ends of the labia minora typically converge at the midline, connected by the  
7 frenulum.  
8

9 The labia minora have been postulated to play a role in the female sexual response (FSR), a complex  
10 interplay of physiological, psychological, and anatomical factors<sup>2-4</sup>. Specifically, the labia minora has  
11 been reported to have rich vascularization and a high concentration of nerve endings, which may  
12 contribute to vascular engorgement and heightened sensation and arousal, respectively, during sexual  
13 activity<sup>5,6</sup>. Yet empirical evidence to link these anatomical characteristics with FSR remains sparse. While  
14 research on the role of the vulvar vestibule<sup>7,8</sup> and clitoris<sup>9,10</sup> in FSR has made significant strides in recent  
15 years, the labia minora has yet to be comprehensively reviewed.  
16

17 Furthermore, individual variations in labial morphology have been widely established, highlighting the  
18 need for a nuanced approach to studying the role of the labia minora in sexual function<sup>11</sup>. While some  
19 women may experience heightened sexual pleasure due to specific anatomical characteristics of their  
20 labia minora, others may encounter challenges related to discomfort or dissatisfaction<sup>2</sup>. The interplay  
21 between anatomical variability and sexual function is complex and warrants investigation to provide  
22 evidence-based insights into clinical practice and sexual health education.  
23

24 In light of these considerations, this paper aims to identify and critically assess the existing literature on  
25 the sexual function of the labia minora, identify gaps in current knowledge, and propose directions for  
26 future research. By elucidating the physiological mechanisms and anatomical correlates of the labia  
27 minora in sexual function, this study seeks to contribute to a comprehensive understanding of female  
28 sexual health.  
29

## 30 **Methods**

31 The objectives, inclusion criteria, and methods for this systematic review were specified in advance and  
32 documented in a protocol<sup>12</sup>. The Preferred Reporting Items for Systematic Reviews and Meta-analyses  
33 extension for Scoping Reviews (PRISMA-ScR)<sup>13</sup> was used to guide the reporting in this study and  
34 standard methods were followed; checklists can be found in Supplementary Table 1. The protocol has  
35 been registered in PROSPERO (CRD42024519600) a priori.  
36

## 37 **Search Strategy**

38 A comprehensive search of the literature was conducted in biomedical, public health, and social science  
39 databases, including PubMed, Web of Science, Scopus, Global Index Medicus, Science Direct, Google  
40 Scholar, Cochrane Library, and HINARI to identify relevant articles published from inception of database  
41 through to March 2024. The final searches were performed in all the databases on March 31, 2024.  
42 Databases were searched using a combination of controlled vocabulary and free text terms for labia minora  
43 and characteristics related to sexual function. Details of the full search strategies are listed in Supplementary  
44 Table 2.  
45

## 46 **Evidence Screening**

47 The eligibility criteria for this scoping review were based on the PCC (Population, Concept, Context)  
48 framework, as recommended by the Joanna Briggs Institute (<https://jbi.global/critical-appraisal-tools>).  
49 Population: Studies involving cis females without congenital abnormalities of the vulva or ambiguous  
50 genitalia. Concept: Studies examining the gross and microscopic anatomy, innervation, vasculature, or  
51 sexual function of the labia minora. Context: Studies conducted across various settings, including clinical,

52 anatomical, and histological studies. No geographical restrictions were applied. Additional eligibility  
53 criteria included peer-reviewed articles, studies in English, and original research (quantitative, qualitative,  
54 or mixed methods). Studies were excluded if they were preprints, conference abstracts, narrative or  
55 literature reviews, case reports, studies not available in English, and those with an unclear methodology or  
56 focus on populations outside the defined eligibility criteria.

57 These criteria were developed to ensure the inclusion of relevant and high-quality studies while maintaining  
58 consistency and replicability.

59  
60 The Rayyan Software (<https://new.rayyan.ai/>) was used to aid in the screening process. Duplicate  
61 publications were immediately excluded. The screening process was conducted in two phases: 1) title and  
62 abstract screening, where two independent reviewers screened all titles and abstracts retrieved from the  
63 database searches to assess their relevance based on the eligibility criteria, and 2) full-text screening where  
64 relevant abstracts were reviewed in full-text format to confirm eligibility. Full-text articles that did not meet  
65 the inclusion criteria were excluded, with reasons for exclusion documented. Conflicts at either stage were  
66 resolved through discussion and, if necessary, adjudication by a third reviewer.

### 67 68 **Data Extraction**

69 Three independent reviewers extracted variables from the full texts of included studies. A full list of  
70 variables extracted can be found in Supplementary Table 3. Data were entered into a 'data charting form'  
71 using Google Forms, which captured general information about the study characteristics, population  
72 demographics, intervention, outcomes, and study design.

### 73 74 **Assessment of risk of bias**

75 Manuscripts were assessed for the quality of evidence using the Oxford Centre for Evidence-Based  
76 Medicine (OCEBM) Levels of Evidence (<https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebmllevels-of-evidence>). This scale grades manuscripts from 1 (highest) to 5 (lowest) based on their study  
77 design. Studies were also assessed using the JBI Critical Appraisal Checklist (<https://jbi.global/critical-appraisal-tools>). Given the scope of this review, which included studies with diverse methodologies, the  
78 combined use of these tools offered a more comprehensive evaluation of evidence quality. The OCEBM  
79 Levels of Evidence provided a hierarchical framework for categorizing studies based on design, while the  
80 JBI checklist ensured a detailed critique of each study's methodological rigor. Together, these tools allowed  
81 for a robust and multidimensional assessment of the included literature, supporting the validity and  
82 reliability of the review findings.

### 83 84 85 86 **Data Analysis**

87 The data analysis focused on systematically organizing and descriptively summarizing the characteristics  
88 and findings of the identified studies to provide a comprehensive overview of the current state of knowledge  
89 on the labia minora and its role in sexual function. We conducted a quantitative, qualitative, and formal  
90 narrative synthesis of the extracted data. Study methodologies, populations, and key outcomes were  
91 tabulated to highlight trends and contextualize findings within the broader research landscape of female  
92 sexual health. A thematic analysis was conducted to identify key patterns across studies, such as anatomical,  
93 vascular, and functional aspects, while also mapping evidence to highlight areas of concentration and  
94 research gaps, including limited exploration of hormonal influences and androgen receptors. Furthermore,  
95 it emphasized the descriptive mapping of evidence and thematic insights. While a risk-of-bias assessment  
96 was performed to enhance rigor, the primary aim was to identify gaps in the literature and provide direction  
97 for future research and clinical practice. By mapping the evidence and summarizing trends, this analysis  
98 contextualizes the findings and underscores areas where further exploration is needed to advance the  
99 understanding of the labia minora within female sexual health.

## 100 101 **Results**

### 102 **Study Selection**

103 The literature search identified 480 entries, which represents 345 unique articles after duplicates were  
104 removed. After abstract screening, 60 articles were included for the full-text review, where 27 articles  
105 matched the inclusion criteria and were included in this review. The PRISMA Flow diagram is illustrated  
106 in Figure 1. All the selected articles were published between 1975 and 2024, described and evaluated the  
107 labia minora. Study characteristics are presented in Supplementary Table 3.

108  
109 **Figure 1.** PRISMA flowchart. Additional information on screening methodology can be found in the  
110 supplementary material.

111  
112 The included studies span a wide range of years, encompassing diverse methodologies and designs to  
113 investigate the anatomy, physiology, and clinical implications of the labia minora. Majority of studies  
114 (n=11) utilized a cross-sectional design (Figure 2A). Data collection methods varied, with the majority of  
115 studies utilizing direct clinical measurements (n=22), followed by surveys or questionnaires (n=12),  
116 imaging techniques such as MRI and ultrasound (n=8), immunohistochemistry (n=4), and observational  
117 approaches (n=3) (Figure 2B). Among the surveys used, the Female Sexual Function Index (FSFI) was the  
118 most frequently employed (n=6 studies), followed by the McCoy Female Sexuality Questionnaire (MFSQ)  
119 (n=5) and the Beck Depression Inventory (BDI) (n=5). These varied approaches reflect the  
120 multidimensional nature of research on the labia minora, addressing both anatomical and psychosocial  
121 factors.

122  
123 The studies were conducted across multiple countries, with the largest number originating in the United  
124 States (n=9), followed by Italy (n=6), Spain (n=5), and Turkey and Germany (n=3 each). Other contributing  
125 countries included Canada, China, France, Egypt, the Netherlands, Sweden, and Czechoslovakia,  
126 highlighting the international scope of research in this field (Figure 3B). Sample sizes varied widely, with  
127 some studies focusing on small cohorts of cadaveric specimens or post-surgical tissues, while others  
128 included larger cohorts of live participants. Of the included studies, 17 focused on participants within  
129 reproductive age (15–50 years), while 9 included subjects outside this age range (Figure 3C). Additionally,  
130 11 studies specifically included menopausal participants, providing valuable insights into the hormonal and  
131 life-stage-related changes in labial morphology and function (Figure 3D).

132  
133 Overall, the risk of bias assessment using the Oxford tool revealed that study quality was mixed, with  
134 variability in methodological rigor across studies. While some studies demonstrated strong methodological  
135 approaches with robust data collection techniques, others had limitations related to sample size,  
136 measurement consistency, and reporting transparency. This heterogeneity in study quality underscores the  
137 need for standardized methodologies in future research on the labia minora.

138  
139 **Figure 2.** Study Design of included studies (A) and type of data collection (B).

140  
141 **Figure 3.** Studies by region. (A) Continent of origin and (B) country of origin. Study population in  
142 reproductive years (C) and menopausal status (D).

### 143 144 145 **Risk of bias of included studies**

146 Although risk of bias assessment is not mandatory for a scoping review, we included it to enhance the rigor  
147 of our analysis by evaluating the credibility of study outcomes. Of the included studies, 37% (10) were  
148 Level 2, 4% (1) were Level 3, 56% (15) were Level 4, and 4% (1) were Level 5. Evidence quality, assessed  
149 using the JBI Critical Appraisal Tool, was generally good, with over 90% of studies scoring “yes” in three  
150 or more domains. 56% (15) of studies received a “high” overall appraisal, 41% (11) were rated as  
151 “moderate,” and 4% (1) as “low.” Detailed quality assessments are provided in Supplementary Table 4.

### 152 153 **Synthesis of results**

154 The main outcomes fell into four themes: anatomy, vascularization, innervation, and sexual function  
155 (Figure 4)

156

157 **Figure 4. Summary and take-home messages of thematic areas identified.**

158

159

160 **Anatomy**

161 Seven articles investigated the anatomy of the labia minora. Two studies used cadaveric specimens<sup>14,15</sup>  
162 and five studies examined live subjects<sup>16-20</sup> with the goal of furthering understanding the anatomy of the  
163 labia minora.

164

165 **Gross Anatomy**

166 Ginger et al. described the gross anatomy of the labia minora using cadaveric specimens, characterizing  
167 the labia minora as folds of tissue situated between the introitus and the labia majora. These folds extend  
168 laterally from the interlabial sulcus to the introitus medially. The study defines the superior aspect of the  
169 labia minora as inserting on the ventral aspect of the clitoral glans or frenulum, with the inferior tip  
170 inserting at the inferior aspect of the vaginal introitus. The labia minora is clearly demarcated from the  
171 labia majora by the absence of adipose tissue in the labia minora, in contrast to the abundant adipose  
172 tissue found in the labia majora<sup>6,14</sup>. It has been hypothesized that the labia minora function to shield the  
173 vestibule from mechanical irritation, dryness, and infections<sup>21,22</sup>. This protective role is attributed to the  
174 fact that the vestibule is derived from endodermal tissue, which is more susceptible to these issues,  
175 compared to the ectodermally derived labia minora, which possess relatively greater structural resilience.  
176 Several studies have explored the asymmetry of the labia minora. For instance, Cao et al. 2021<sup>15</sup> used  
177 cadaveric specimens and discarded labial tissue to report that 67% of their study population exhibited  
178 asymmetry. Conversely, Kaya et al. 2018<sup>18</sup> found that 31.5% of the 89 participants had asymmetry, while  
179 68.5% had symmetric labia minora. Cao et al. 2021<sup>15</sup> based their findings on cadaveric specimens and  
180 discarded tissue samples whereas Kaya et al. 2018<sup>18</sup> collected measurements from live participants. The  
181 use of cadavers and surgically removed tissues can impact measurement accuracy, as tissue shrinkage and  
182 size changes can occur post-mortem and after the cessation of perfusion. Additionally, these studies did  
183 not clarify whether peri or postmenopausal patients were included, which could be significant, as  
184 vulvovaginal atrophy due to estrogen loss in this population may influence labial size<sup>23</sup>. The inconsistency  
185 in asymmetry findings across studies underscores the need for further research to determine the  
186 prevalence of labial asymmetry accurately. The Kaya et al. 2018<sup>18</sup> study had limitations, including the  
187 exclusion of three patients with asymmetric labial diameters who did not meet inclusion criteria.  
188 Additionally, only six patients in this study had a labium minus width of 40 mm or more, potentially due  
189 to the study population's composition, which primarily consisted of patients seeking interventions for  
190 non-cosmetic gynecological reasons. This may have led to an underestimation of the prevalence of labial  
191 asymmetry in the general population.

192

193 **Labia Minora Width**

194 The width of the labia minora has been assessed using various methods, including digital calipers<sup>16</sup>, 2D  
195 US imaging<sup>19,20</sup>, and 2D MRI imaging<sup>17</sup>. Studies have reported significant variability in labial width,  
196 influenced by factors such as age, hormonal status, and individual anatomical differences<sup>23,24</sup>. For  
197 instance, Cao et al. 2021<sup>15</sup> reported mean labial widths of  $20.94 \pm 6.50$ mm (left) and  $20.11 \pm 5.92$ mm  
198 (right) in cadaveric specimens, but the lack of age stratification limited the interpretation of how these  
199 dimensions change across life stages (Table 1). This omission is significant given the known changes in  
200 labial anatomy during puberty and the regression that occurs during and after menopause<sup>23,24</sup>. In contrast,  
201 Suh et al. 2004<sup>17</sup> observed age-related differences, with premenopausal women having wider labia ( $11 \pm 2$   
202 mm) compared to postmenopausal women ( $9 \pm 2$  mm), consistent with vulvovaginal atrophy due to  
203 decreased estrogen levels. These findings align with the well-documented trend of vulvovaginal atrophy  
204 and a decrease in tissue size following menopause<sup>23</sup>.

205  
206 Kaya et al. 2018<sup>18</sup> conducted a study measuring labia minora width bilaterally, dividing the labia into  
207 three sections based on the Banwell classification<sup>25</sup> and utilized the Mokatef classification<sup>26</sup> to categorize  
208 labial protrusion (Table 1). Notably, there is a large range and variation in the natural size of the labia  
209 minora that has been reported in the literature, and it has also been observed that the size of the labia can  
210 change over time<sup>11,27</sup>. The fact that the patient population in the study analyzed were majority multiparous  
211 and study design lacked stratification by participant weight could introduce confounding variables. Such  
212 studies emphasize the need for broader investigations to better characterize labial anatomy and its natural  
213 variations. A more detailed exploration of labial asymmetry, which is commonly observed, is also  
214 warranted. Many women present with asymmetrical labia, yet societal and cultural norms often label  
215 these differences as "abnormal," contributing to misconceptions about female genital anatomy. Future  
216 research should seek to clarify the range of labia minora width in order to demedicalize non-pathological  
217 labia and educate the public on diverse genital appearance.

218  
219 The concept of labial asymmetry, while physiologically normal and widely prevalent, has not been  
220 adequately addressed in clinical or public discussions; many women are unaware of the wide variability  
221 in normal anatomical structures. This lack of awareness can contribute to psychological distress, as  
222 women may feel pressured to conform to unrealistic ideals of genital appearance. Such distress can  
223 negatively impact sexual self-esteem and overall sexual health. Vulvar psychology, particularly as it  
224 relates to perceptions of "normalcy," plays a critical role in shaping sexual self-esteem and may in part  
225 contribute to an increase in demand for labiaplasty. While labiaplasty can alleviate discomfort caused by  
226 hypertrophic labia during physical activities or intercourse, it is often sought to achieve an idealized  
227 appearance. A detailed discussion of the motivations for labiaplasty, its outcomes, and its potential impact  
228 on sexual self-esteem is essential. Clinicians must adopt a patient-centered approach when addressing  
229 concerns about labial appearance, emphasizing the natural diversity of genital anatomy and dispelling  
230 harmful stereotypes. Public health education campaigns can play a critical role in normalizing labial  
231 variability and promoting body positivity.

232  
233 Interestingly, several intrinsic factors have been reported to affect the width of the labia minora. Battaglia  
234 et al. 2012<sup>19</sup> observed that labia minora thickness varied across the menstrual cycle, with measurements  
235 taken during the follicular phase being significantly smaller than during the periovulatory phase. This  
236 finding suggests a positive correlation between estradiol levels, which peak around the periovulatory  
237 phase, and labia minora thickness. Estradiol's effect on labial thickness may be explained by its  
238 enhancement of nitric oxide (NO) production through increasing expression and activity of endothelial  
239 nitric oxide synthase (NOS)<sup>28</sup>. NO subsequently raises cGMP levels and allows calcium influx into the  
240 vascular labia minora, causing vasodilation and resulting in labial engorgement<sup>17</sup>. However, studies have  
241 observed a significant decrease in labia minora thickness after three months of treatment with a  
242 combination oral contraceptive pill (OCP) containing 30mg ethinylestradiol and 3mg drospirenone<sup>29</sup>.  
243 While estriol is associated with increased labia minora thickness, the exogenous administration of  
244 combination estrogen and progestin, like drospirenone in OCPs, has the opposite effect. OCP-induced  
245 hypoestrogenism is well-documented<sup>30-32</sup>, and linked to an increased resistance of the posterior labial  
246 artery, contributing to reduced labial thickness<sup>20</sup>. Furthermore, OCPs are known to lower androgen levels,  
247 which may further reduce labial thickness, though the role of androgens in labia minora morphology  
248 remains unclear<sup>33,34</sup>. Further research is needed to elucidate androgen influence on the anatomy and  
249 physiology of the labia minora.

250  
251 One study investigated labia minora width in regards to the FSR, where labia minora width was measured  
252 before and after arousal induced by an erotic film<sup>17</sup>. They found that labia minora width increased  
253 significantly in both pre- and postmenopausal women, as well as MRI signal enhancement. However, it is  
254 important to consider that the study used only psychogenic stimuli (an erotic film) to induce arousal,

255 which may have affected the degree or capacity of arousal achieved by participants, potentially  
256 influencing the results.

257

### 258 ***Microanatomy Histological Characterization***

259 Five studies investigated the microanatomy of the labia minora tissue through histological  
260 characterization<sup>5,6,14,35,36</sup> (Table 2). From cadaveric and discarded surgical tissue samples, the labia minora  
261 is consistently described as being lined by stratified squamous epithelium with papillary protrusions, and  
262 melanocytes distributed throughout the basal layer of the epithelium<sup>5,15</sup>. The epidermis of the labia minora  
263 comprises four layers: the basal layer, spinous layer, granular layer, stratum corneum, and a superficial  
264 cornified layer. Beneath this, the dermis was reported to have a papillary structure with fine collagen,  
265 reticular, and elastic fibers, and a deeper reticular layer with collagen and elastic fibers<sup>5</sup>. Sebaceous  
266 glands and eccrine sweat glands were also identified, with openings to the skin's surface through  
267 sebaceous glands. In postmenopausal women, the labia minora epithelium was found to be more thinly  
268 keratinized<sup>6</sup>. The labia minora were also noted to have an abundance of elastin fibers and a lack of  
269 smooth muscle, thought to be related to the labia minora's function in engorgement during sexual  
270 arousal<sup>6,14</sup>.

271 Martin-Alguacil et al. 2008<sup>35</sup> conducted immunohistochemical (IHC) staining to investigate estrogen  
272 receptor (ER) expression in the labia minora. They found ER- $\alpha$  staining on cell membranes of fibroblasts  
273 as well as basal and suprabasal epidermal cells in the superficial labia minora, and ER- $\alpha$  nuclear staining  
274 in the stroma localized superiorly near the clitoris<sup>35</sup>. ER- $\beta$  staining was more concentrated in the basal  
275 epidermal and apocrine glandular epithelial cell membranes (Table 2). Clinical implications of these  
276 findings are demonstrated through a case report of a 29-month-old girl from Italy who presented with  
277 labial adhesions which were resolved with topical estriol<sup>37</sup>. Although the precise pathophysiology of  
278 labial adhesions remains unclear, they are thought to develop due to the low endogenous estrogen in  
279 young girls, exacerbated by the thin and immature nature of the labia minora<sup>38</sup>. The patient's favorable  
280 response to estriol 0.05% cream underscores the presence of estrogen receptors in the labia minora and  
281 suggests a potential treatment approach for labial adhesions in young, prepubertal girls<sup>35</sup>. It is important to  
282 note that research on the presence of androgen receptors in the labia minora is scarce. Hodgins et al.  
283 1998<sup>39</sup> reports androgen receptors in the epidermis of labia minora, but further characterization and  
284 understanding of clinical implication is largely lacking.

### 285 **Vascularisation**

#### 286 ***Blood Vessel Morphology***

287 Vascularization of the labia minora was investigated by five papers<sup>15,18,40-42</sup>. Collectively, these studies  
288 report four main arteries supplying the labia minora: a central dominant vessel along with two posterior  
289 arteries and one small anterior artery, all of which anastomose along the edge of the labia minora<sup>15,18,40-42</sup>.  
290 The origin of the blood supply involves the external and internal pudendal arteries in creating  
291 anastomoses<sup>15,18,42</sup>. The external pudendal artery is described as the communication between the posterior  
292 labial arteries, where two additional collateral arteries communicate between this posterior system and the  
293 internal pudendal artery on the anterolateral aspect of the labia minora<sup>42</sup>. Moreover, the external pudendal  
294 artery plays a role in the perfusion of the clitoris and communicates with the posterior system via the  
295 frenulum arteries, connecting blood supplies at the mucosal surface of the anterior part of the labia  
296 minora<sup>42</sup>. Additionally, the superficial pudendal artery was observed to supply both the skin of the labia  
297 minora and the foreskin of the clitoris<sup>15,18</sup>. Regarding the anatomic journey of the blood vessels through  
298 the labia minora, the dominant central artery is reported to project perpendicular to the long axis of the  
299 labia minora<sup>42</sup>. When the edge of the labia minora is reached, the artery continues coursing under the edge  
300 in a posterior to anterior direction, fading as the anterior part of the labia minora is reached<sup>18,42</sup>. The edge  
301 artery is characterized as the anastomosis between anterior and posterior arteries<sup>18</sup>. Lack of coloration of  
302 the most anterior part of the labia minora with latex injection suggests that the more anterior labia minora  
303 represents the least perfused part<sup>42</sup>. The two posterior arteries and the smallest anterior artery were

304 reported to have a perpendicular trajectory to the long axis of the labia minora<sup>42</sup>. Finally, the base artery is  
305 at the introitus indicating anastomosis with the internal pudendal artery<sup>18</sup> (Figure 2).

306  
307 To investigate labia minora arterial morphology one study used cold light illumination to assess whether  
308 the central dominant labial artery coursed medially, superior, or posterior, as well as any differences  
309 between left and right labia minora<sup>18</sup>. The authors reported that in 93.3% (n=83) of all cases, regardless of  
310 whether the artery was medial, superior, or posterior, the artery was observed on the right labia minora<sup>18</sup>.  
311 The significance of having right-sided-dominant arteries is unclear, and further research should  
312 investigate whether there are any functional anatomical or clinical implications associated with right  
313 versus left-sided arterial prominence. One limitation of this study is that in using cold light illumination it  
314 is not possible to precisely distinguish between arteries and veins, introducing potentially biased results.  
315 A study performing contrast dye injection and rotational angiography on fresh cadavers investigated labia  
316 minora arteries emergence<sup>42</sup>. The authors reported that the central artery typically emerges around the  
317 midpoint of the labia minora, at about the 55th percentile of its length. The two posterior arteries emerge  
318 closer to the posterior end, at the 17th and 32nd percentiles<sup>42</sup>. Lastly, the small anterior artery is located  
319 towards the anterior end, at the 76th percentile of the labia minora's length<sup>42</sup>.

320  
321  
322 **Figure 5.** Vascular Morphology of the Labia Minora. 1: Branch of external pudendal, 2: Superficial  
323 pudendal, 3: Edge artery, 4: Anterior artery, 5: Central dominant artery, 6: Posterior artery, 7: Base artery,  
324 8: Branch of internal pudendal.

325  
326

### 327 *Microanatomy and Histology of Vasculature*

328 Microanatomy investigation of the labia minora has provided insight into its vasculature characteristics.  
329 Authors consistently report that the labia minora contains vascular tissue immediately deep to the  
330 epithelium, and is composed of vessels embedded in fibrous tissue rather than smooth muscle<sup>6,14</sup>. The  
331 tissue contains variably-shaped vascular spaces, which are postulated to accommodate volumes of blood  
332 during arousal<sup>14</sup>, supported by MRI studies<sup>6</sup>. These findings were consistent regardless of menopausal  
333 status<sup>6</sup>. Moreover, PDE4 markers were reported in vascular labia minora tissue, with significant PDE4  
334 expression observed in the arterioles of the subepithelial layer and PDE5 expression in the vascular  
335 smooth muscle<sup>43</sup>(Table 2). PDE4 has been shown to contribute to endothelial and epithelial barrier  
336 stability<sup>44</sup>. In contrast, PDE5 in vascular smooth muscle degrades cGMP, allowing vasorelaxation; in  
337 penile arteries during male erection inhibition of PDE5 allows cGMP to accumulate and activate a  
338 cascade of downstream phosphorylation and dilation of blood vessels<sup>45</sup>. However, whether the roles of  
339 PDE4 and PDE5 in the vasculature of the labia minora function similarly to their roles in the penis is  
340 unclear. Further research is needed to clarify their specific functions and significance in labia minora  
341 physiology.

342  
343 The vasculature of the venous system has received far less attention than the arterial network. Venous  
344 distribution has been described as having similar anastomotic branching in the same direction as  
345 arteries<sup>15</sup>. Additionally, deep veins from Kobelt's plexus are reported to penetrate the tunica albuginea of  
346 the clitoral cavernosa, traversing the angle of the clitoris between the glans and the corporal bodies,  
347 meeting the lamina propria of the anterior vestibule<sup>36</sup>. Kobelt's plexus and the surrounding stroma form  
348 the pars intermedia, a key structure in the sexually responsive nonerectile tissues of the labia minora,  
349 coordinating differential drainage following sexual arousal and engorgement<sup>36,46</sup>. Future research should  
350 investigate the FSR as it relates to venous drainage during arousal and orgasm, compared to basal  
351 conditions.

### 352 353 *Clinical Implications*

354 Three articles in our review emphasize the critical importance of accurately identifying vascular  
355 morphology when planning surgical procedures involving the labia. Kaya et al. 2018<sup>18</sup> stratified patients  
356 based on the upper, middle, or lower position of the central artery in the labia minora, finding a  
357 significantly higher percentage of the central vessel in labia with an upper morphology compared to those  
358 with a lower morphology<sup>18</sup>. This highlights the need to consider the extent of central vasculature  
359 disruption during surgery. For example, labiaplasties, which are often performed using a wedge resection  
360 technique, require a choice between anterior, posterior, or central wedge approaches<sup>47</sup>. In labia with a  
361 lower morphology, the central vessel is located lower, with the posterior vessel branching from it<sup>18</sup>. A  
362 posterior wedge resection in these cases can severely disrupt blood flow by cutting the main artery.  
363 Conversely, in labia with a middle morphology, the posterior vessel is positioned higher, increasing the  
364 risk of cutting the central vessel during a central wedge resection. These findings underscore the  
365 importance of tailoring surgical techniques to each patient's specific vascular map to optimize outcomes  
366 and minimize bleeding risks during labiaplasties. In addition to wedge resection, another labiaplasty  
367 technique is de-epithelialization. It was first proposed by Choi et al. 2000<sup>48</sup> that a wedge excision  
368 sacrifices major vessels which may result in dehiscence, and that a de-epithelialization technique solves this  
369 problem<sup>48</sup>. However, Choi assumed that with de-epithelialization, the labial vessels are preserved. The more  
370 recent findings of Georgiou et al. 2015<sup>42</sup> reported that the arteries of the labia minora run just under the  
371 mucosa of the skin and not in the central core of the labia minora, such that even de-epithelialization may  
372 interrupt these vessels. Having this model in mind, labiaplasty techniques should be discussed in terms of  
373 arterial flow preservation. It is crucial to understand the implications of surgical interventions and the  
374 potentially life-altering complications that can arise if individualized vascular morphology is not  
375 considered.

### 376 377 **Innervation**

378 Critical to understanding the functional and clinical importance of the labia minora is comprehensive  
379 knowledge of its innervation. Of the 26 papers we included, 14 focused on the innervation of the labia  
380 minora. Among these, five analyzed cadaveric specimens<sup>14,15,42,49,50</sup>, seven examined surgical  
381 specimens<sup>5,15,40,50-53</sup>, and five examined live human subjects<sup>40,41,54-56</sup>. Various methods were used to  
382 evaluate neuroanatomy: six papers employed immunohistochemistry<sup>5,15,35,49,52,53</sup>, three used gross  
383 anatomical observation and measurements<sup>14,40,51</sup>, one utilized radiologic imaging<sup>42</sup>, one conducted nerve  
384 conduction studies<sup>56</sup>, two performed sensory testing<sup>54,55</sup>, and three performed qualitative assessments of  
385 sensation<sup>40,41,57</sup>.

### 386 387 **Gross anatomy**

388 A cadaveric study using computed tomography with contrast suggested that the neuroanatomy of the labia  
389 minora originates from the pudendal nerve<sup>42</sup>. Though the sample size was small (n=9), the anatomy found  
390 was consistent in all cases observed. Two studies found that once neural branching occurs in the labia  
391 minora, the network is largely concentrated to a central neural core extending the length of the labia  
392 minora and traveling alongside vascular structures<sup>14,15</sup>. Indeed, nerve count has been reported higher in  
393 the medial region than the lateral region<sup>15</sup>, with higher overall nerve and nerve bundle density in the  
394 superior middle region of the labia minora<sup>40,49</sup>.

### 395 396 **Nerve Endings**

397 In the labia minora, sensory nerve endings are reported to include free nerve endings, arborizations,  
398 spray-like endings, clew-like nerve endings, and Pacinian-like corpuscles<sup>50</sup>. A collective hypothesis from  
399 three independent studies has emerged that labia minora central core nerves are predominantly clew-like  
400 formed by one or more thick branching myelinated afferent axons with large nucleated Schwann cells and  
401 small nerve fibers toward the edges<sup>14,15,50</sup>. The average length of clew-like endings was reported to be  
402 256µm with an average width of 199µm, where thickness and variation in nerve endings were  
403 independent of age<sup>50</sup>. Free nerve endings, identified via Cajal-type silver staining, were found to pass  
404 through the dermis and terminate in the stratum granulosum, basale, and spinosum of the epidermis<sup>5</sup>.

405 Nerve density was reported to be most concentrated at the subepithelial plexus as well as at basal and  
406 spinous layers of the exterior epithelium<sup>5</sup>. Interestingly, in a study examining the sensory nerve endings in  
407 hypertrophic labia minora, the rate of occurrence of genital corpuscles was significantly higher (28.43%)  
408 in hypertrophic labia, compared to control (10.2%), which the authors suggest to be indicative that  
409 hypertrophy may be related to an underlying growth factor that induces nerve growth<sup>51</sup>.

410

#### 411 ***Histological Molecular Characterization***

412 Immunostaining of the labia minora has consistently reported peripheral Pacinian-like corpuscle of the  
413 labia minora<sup>5,15,50,53</sup>. The corpuscle itself, initially elucidated by Mason's trichrome, demonstrated an axon  
414 surrounded by an inner core with 5HTT and neuropeptide Y (NPY), outer core with positive PGP 9.5,  
415 5HTT, 5HT1A, neuron specific enolase (NSE), and ER $\alpha$ , and an external capsule with PGP 9.5, neuronal  
416 nitric oxide (nNOS), and ER $\alpha$  positive staining<sup>53</sup> (Table 3). PGP 9.5, NPY, and NSE are all nerve-specific  
417 markers, while 5HTs are serotonin receptors, and nNOS is a vasodilator and mediator of synaptic  
418 plasticity. Evidently, neuroprotection, neurodegeneration, and neurovascular interplay of the labia minora  
419 appear to be serotonin, estrogen, and nitric oxide mediated. Interestingly, nNOS and S-100, a neural  
420 marker, stain more intensely and widespread at the introital border versus the exterior border of the labia  
421 minora<sup>5,35</sup>. Subsidiary innervation in the stroma was positive to VIP and NPY<sup>53</sup> (Table 3). NPY is a  
422 pleiotropic peptide involved in vasoconstriction and inflammation<sup>58,59</sup>. Various dermatologic pathologies  
423 are partially explained by genetic variations in NPY and modulated by inflammatory stress<sup>60</sup>. VIP also  
424 acts as an immunoregulator<sup>61</sup>. Variations in the genetic disposition of these peptides may have a role in  
425 labia minora function such as immunomodulated dermatose pathologies, highlighting the need for further  
426 investigation to improve clinical diagnosis and outcomes.

427

#### 428 **Consolidation of Sexual Function Evidence of the Labia Minora**

429 Integral to the fundamental understanding of the labia minora is a thorough understanding of their role in  
430 sexual function. Despite this importance, this review identified limited literature focused on defining their  
431 sexual function; of the 28 papers included in this study, ten examined sexual function. Among these, nine  
432 used questionnaires: four studies used the Female Sexual Function Index (FSFI)<sup>16,40,41,54</sup>, three studies  
433 used the McCoy Female Sexuality Questionnaire (MFSQ)<sup>20,29,62</sup>, one study used both FSFI and MFSQ<sup>63</sup>,  
434 and one study used the Index of Female Sexual Function<sup>55</sup>. While most studies used a questionnaire to  
435 evaluate sexual function, few focused on the sexual function of the labia minora, and instead examined  
436 the relationship between lifestyle or comorbidities (pregnancy, diabetes, alcohol, smoking, oral  
437 contraception) on sexual function. Six papers posited connections to the possible roles of the labia minora  
438 in sexual function based on original physiological evidence<sup>16,20,53,62-64</sup>.

439

440 The finding of abundant clew-like and pancinian-like corpuscles to the labia minora suggests their role as  
441 sensory organs crucial to female sexual arousal<sup>53</sup>. Pacinian corpuscles are well-known for their role in  
442 sensory perception and rapid response to pressure, and similar corpuscles have been identified in the  
443 clitoris, the primary organ involved in sexual arousal<sup>65,66</sup>. The finding that these labia minora corpuscles  
444 contain ERs, indicates that hormonal fluctuations—such as those occurring during the menstrual cycle,  
445 pregnancy, or menopause—could influence their function, potentially altering the labia minora's ability to  
446 become aroused, engorge with blood, and participate in the FSR<sup>53</sup>.

447

448 Two studies analyzed the pulsatility index (PI) of the labial artery in association with sexual function<sup>20,63</sup>.  
449 The PI is a non-invasive method of assessing vascular resistance with Doppler ultrasonography<sup>67</sup>. One  
450 study found that as the PI of the posterior labial artery decreased, the labia minora thickness increased,  
451 indicating that lower resistance in the labial artery allows for easier engorgement, leading to the observed  
452 increase in labial thickness<sup>63</sup>. Further, as the labia minora became thicker, so too did the patient-reported  
453 frequency of intercourse, purported to be due to increased arousal of the genital tissues<sup>63</sup>. A different  
454 study examining smoking and sexual function via Doppler histogram analysis of labia minora  
455 vascularization, reported that the labia minora PI progressively increased from non-smokers to current

456 heavy smokers ( $p \leq 0.01$ )<sup>20</sup>. As a high PI is associated with increased vessel resistance and thereby  
457 decreased engorgement function, it was concluded that current heavy smokers may experience a  
458 decreased FSR due to impeded vascularity, likely attributed to atherosclerosis of labial arteries from  
459 carcinogens<sup>20</sup>. Taken together, these findings indicate a link between vascular responsiveness in the labia  
460 minora and sexual function, suggesting that PI may be a useful tool in assessing the FSR of the labia  
461 minora.

462  
463 A cohort study involving two groups watching a neutral and erotic film in different orders examined labia  
464 temperature changes to explore the sexual function of the labia minora.<sup>54</sup> The study found that  
465 participants who watched the neutral film first experienced a significantly higher increase in labia  
466 temperature during the erotic film compared to those who watched the erotic film first<sup>54</sup>. This suggests  
467 that initial exposure to neutral stimuli may maximize sexual response, possibly due to increased comfort  
468 in the testing environment or a lack of baseline sensory testing. The study also indicated that the labia  
469 minora plays a role in sexual arousal, as the observed temperature increase correlates with increased  
470 blood flow<sup>54</sup>. However, the study's focus on pain response rather than pleasure may have skewed the  
471 results, and further research is needed to clarify the link between labia minora temperature, blood flow,  
472 and sexual function.

473  
474 One study used the modified Clark oxygen electrode to examine the difference in labia minora arterial  
475 blood flow between basal, self-stimulation, and orgasm, utilizing pO<sub>2</sub> levels<sup>64</sup>. This study reported that  
476 from baseline levels ( $18.3 \pm 3.7$  mmHg), upon initiation of sexual self-stimulation, there was a significant  
477 increase in oxygen tension in the labia minora which peaked ( $47.3 \pm 4$  mmHg) immediately after orgasm  
478 began<sup>64</sup>. Once the orgasm ended, there was a decrease in oxygen tension in the labia minora, but post-  
479 orgasm oxygen tension in the labia minora remained higher than at baseline levels for 20-30 minutes<sup>64</sup>.  
480 Given the substantial changes in pO<sub>2</sub> in the labia minora before and after orgasm, these findings suggest a  
481 role of pO<sub>2</sub> in the labia minora and sexual function. Namely, it is possible to infer that the labia minora  
482 could support an increase in blood flow and engorgement function in the FSR. Further investigation is  
483 needed to understand how the changes in vasculature of the labia minora contribute to orgasm.

484  
485 Overall, most of the data examining the sexual function of the labia minora focused on blood flow, and  
486 other ways that the labia minora may impact sexual function have been largely ignored. Additional  
487 studies are needed to explore the possibility of changes in labia minora function, sensitivity, and  
488 innervation attributed to pacinian-like corpuscles with serotonin and ER receptors. Furthermore, research  
489 related to altered hormonal state should be investigated, and the presence of androgen receptors in should  
490 be investigated. Additionally, the order of blood flow between the labia and clitoris, and the relationship  
491 between the two needs to be better understood. It is unclear whether blood flows sequentially or in  
492 parallel, or if blood flow from the labia facilitates blood flow to the clitoris and vice versa.

#### 493 **Labia Minora Over a Lifetime**

494  
495 The labia minora undergo significant changes throughout a woman's life, starting as almost absent in the  
496 prepubertal stage, growing in size during puberty, and eventually resorbing during menopause<sup>24</sup>. This  
497 pattern of growth and regression has not been extensively studied, leaving a gap in our understanding of  
498 its physiological and developmental significance. Notably, the development of the median raphe in males,  
499 which forms early in fetal life, suggests a possible role of androgens in the development of the labia  
500 minora, given that the labia minora is the female homologue to the median raphe<sup>69,70</sup>. This hypothesis is  
501 further supported by observations in patients with congenital adrenal hyperplasia (CAH), who may offer  
502 valuable insights into the androgenic influences on labia minora development and function<sup>71-73</sup>. These  
503 observations underscore the need for further research to explore the hormonal and developmental factors  
504 influencing the labia minora across different life stages.

#### 505 **Limitations**

507 The included studies in this review present several limitations that highlight the need for further research.  
508 Methodological variability, such as differences in study designs—ranging from cadaveric to live subject  
509 studies and imaging versus histological techniques—complicates cross-comparisons of findings.  
510 Population biases are evident, with many studies relying on small or non-representative samples, such as  
511 cadaveric tissues or patients undergoing surgery for unrelated reasons. The reliance on cadaveric  
512 specimens, in particular, introduces potential limitations, as post-mortem changes such as tissue  
513 shrinkage, loss of vascular perfusion, and alterations in tissue elasticity may not accurately reflect the  
514 functional anatomy observed in living individuals. These factors can lead to under- or overestimation of  
515 measurements, particularly in studies examining vascularization and innervation. Furthermore, few  
516 studies stratified results by age or menopausal status, limiting understanding of how labial anatomy and  
517 function evolve across different life stages. Notably, there is evidence that the anatomy of the labia  
518 minora varies significantly depending on age and hormonal status, with changes such as decreased tissue  
519 size and vascularization observed in postmenopausal individuals. These variations underscore the need  
520 for a more in-depth discussion of how life stage, hormonal environment, and sample type influence labial  
521 morphology and function.

522  
523 To address these gaps, future research should focus on comprehensive anatomical studies to establish  
524 population-based data on labial asymmetry, size variations, and normative ranges across ages and  
525 hormonal statuses. Investigating the relationship between androgen exposure and labial development,  
526 particularly in conditions like congenital adrenal hyperplasia (CAH), could offer valuable insights.  
527 Advanced imaging modalities, such as Doppler ultrasonography and angiography, could be employed to  
528 map arterial and venous systems under different physiological and hormonal conditions. These  
529 approaches would also help elucidate the interplay between labial and clitoral blood flow in sexual  
530 response. Understanding the functional roles of nerve endings and hormonal receptors, including  
531 estrogen, serotonin, and nitric oxide, in sensory function and arousal is equally crucial. Clinical  
532 correlations, such as the impact of labial morphology on sexual satisfaction and function, warrant  
533 exploration using validated tools like the Female Sexual Function Index (FSFI). Additionally, surgical  
534 guidelines must incorporate individualized vascular and neural maps to minimize complications during  
535 labiaplasty and other interventions, while non-surgical treatments for labial adhesions and atrophy should  
536 leverage hormonal and neurochemical insights.

537  
538 Finally, limitations inherent to the scoping review methodology must be acknowledged. Exclusion of  
539 non-English studies may have omitted relevant findings from other regions, and the omission of grey  
540 literature, preprints, and conference abstracts may have narrowed the scope of included evidence.  
541 Moreover, as a scoping review, the focus was on mapping evidence rather than conducting in-depth  
542 synthesis or quantitative meta-analysis, limiting insights into specific outcomes. Nonetheless, by  
543 addressing these limitations and pursuing interdisciplinary, targeted research, future studies can deepen  
544 understanding of the labia minora's anatomy and function. This is particularly important for examining  
545 differences influenced by age, hormonal factors, and the type of specimen studied, improving clinical  
546 practices and advancing female sexual health.

## 547 548 **Conclusion**

549 In summary, the labia minora likely plays a critical, but poorly understood, role in FSR. Studies have  
550 brought attention to rich vascularization and innervation patterns of the tissue, and their potential  
551 involvement in FSR through engorgement and sensory functions. Despite these insights, significant  
552 knowledge gaps persist, particularly concerning whether the anatomy of blood vessels is dependent on an  
553 individual's unique labial morphology (right vs left dominant, upper vs low prominence), the exact  
554 innervation pathways and locations of nerves, and the effect of androgens on the labia minora. This lack  
555 of knowledge impedes comprehension of these vital structures and hampers the ability to optimize  
556 procedures to minimize bleeding and prevent nerve damage. Additionally, the development of effective  
557 therapeutic interventions for vulvar-associated pathologies is compromised. Without a comprehensive

558 understanding, clinicians and researchers lack the necessary insights to develop treatments that preserve  
 559 the function and overall well-being of affected individuals. Future research should prioritize detailed  
 560 anatomical and physiological studies to fully explore the labia minora's role in FSR. Gaining deeper  
 561 insights into the labia minora will enhance our knowledge of female genital anatomy and sexual health,  
 562 helping to prevent complications and improve the diagnosis and treatment of related disorders.

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Author	Population Characteristics	Pre-/Post Menopausal	Method of Measurement	Mean Width (mm)	Significance
Cao et al 2021 <sup>15</sup>	Cadavers (n=7): 47yo  Discarded Labia Minora Tissue (n =18): 28.89 yo	Postmenopausal	Not specified	Right labium minora width: 20.11 ± 5.92  Left labium minora width: 20.94 ± 6.50	No hypothesis testing done
Kaya et al. 2018 <sup>18</sup>	Patients who underwent any gynecological intervention excluding aesthetic genital surgery  (n= 89) 34.3 +/- 8.6 yo	pre- and postmenopausal	Not specified	Right labium minus width: 0-20mm, 51.7% 20-40mm, 47.2% >40mm, 1%  Left labium minus width: 0-20mm, 16% 20-40mm, 41.6% >40mm,4%	p = 0.017  p = 0.069
Kaya et al. 2020 <sup>16</sup>	Healthy, non-pregnant, no OCP or IUD use  (n=208) 35.2 +/- 9.1	premenopausal	Digital stainless-steel Vernier caliper	Right labium minora width: 21.2 ± 8.6  Left labium minora width: 22.0 ± 9.6	No hypothesis testing done
Suh et al 2004 <sup>17</sup>	Healthy Women  Premenopausal (n=11): 30.3 years  Menopausal (n=8): 56.4 years	pre-and postmenopausal	2D MRI	Labia minora, Premenopausal: Neutral: 11 ± 2 During arousal: 13 ± 2  Labia minora, Menopausal: Neutral: 9 ± 2 During arousal period: 10 ± 2	p < 0.01  p < 0.01

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 571 **Table 1.** Summary of results from studies on labia minora width  
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Author	Sample	Method	Marker	Findings
Schober et al 2010 <sup>52</sup>	Waste tissue strips from the surgical separation of the labial fusion of 10 girls 2-9y/o	Waste tissue strips from the surgical separation of the labial fusion of 10 2-9y/o girls were taken. Tissue was stained with Masson's and Hematoxylin and Eosin, fixed, frozen and cut into 30µm sections.	H&E	Labia minora are lined by Stratified squamous epithelium. Epidermis has the typical 4 layers (basal, spinous, granular, and stratum corneum). The dermis is differentiated into papillary and reticular, with the latter containing vascular and lymphatic plexus surrounded by collagen and elastic fibers. The papillary was composed of fine collagen, elastic, and reticular fibers. Connective tissue papillae from this layer sometimes projected into the epithelium. Labia minora has dense sebaceous glands and eccrine sweat glands that open onto the skin.
Shih et al. 2013 <sup>36</sup>	9 cadaveric female vulvectomy specimens	Samples were embalmed and buffered in formalin for processing. All vulvectomy specimens were serially sectioned and submitted in separate cassette blocks. Serial sections were then stained with H&E to examine general histologic features.	H&E	The pars intermedia is composed of predominantly collagen-rich stroma supporting the veins of Kobelt's plexus, traveling longitudinally in the angle of the clitoris. Observed non-erectile specialized vascular tissue of the labia minora, which allows differential drainage following sexual arousal and engorgement to occur.
Martin-Alguacil et al. 2008 <sup>35</sup>	Waste tissue strips from the surgical separation of the labial fusion of 10 girls 2-9y/o	Labial tissue was fixed in 4% paraformaldehyde, bugged, frozen and cut into 30µm thick sections. The specimens were incubated with rabbit anti-ER alpha, rabbit anti-ERbeta, and rabbit anti-nNOS. The sections were then processed in rabbit IgG Vectastain ABC Kit.	ERα	ERα present in the stroma of the labia minora near the clitoris and basal and suprabasal epidermal cells membrane in superficial labia minora
			ERβ	ERβ stained positively in the cell membrane basal and suprabasal epithelial cells as well as apocrine glandular epithelial cell membrane superficially. Lamina propria contained ERβ positive fibroblasts.
			nNOS	nNOS was diffusely distributed and corresponded with nerve bundles and fibers in the stroma of the labia minora.
Martin, Alguacil et al. 2011 <sup>33</sup>	Waste tissue strips from the surgical separation of the labial fusion of 10 girls 2-9y/o	Labial tissue was fixed in 4% paraformaldehyde, bugged, frozen, and cut into 30µm thick sections. The specimens were incubated with rabbit anti-ERα, and rabbit anti-ERβ. The sections were then processed in rabbit IgG Vectastain ABC Kit	ERα	ERα present in the outer core, external capsule, and stroma of the Pacinian-like corpuscle of the labia minora
			ERβ	ERβ stained positively in the stroma of the Pacinian-like corpuscle of the labia minora
Uckert et al. 2007 <sup>43</sup>	Human labial tissue was obtained from 4 fresh female cadavers.	Vibratome sections prepared from formaldehyde fixed tissue specimens, and incubated with primary antibodies against PDE isoenzymes. Sections were then incubated with fluorochrome (fluorescein isothiocyanate, Texas Red)-labeled secondary antibodies. Visualization was commenced using a laser fluorescence microscope.	PDE3	PDE3 was widespread in epithelial layer cells, epithelial sebaceous glands, and neuroendocrine labial epithelium cells
			PDE4	PDE4 was diffusely present but prominent in arterioles throughout the subepithelial layer as well as vascular smooth muscle and vascular endothelium
			PDE5	PDE5 was prominent in the vascular smooth muscle
			PDE11	PDE11 was mainly registered in epithelial glandular-like structures

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**Table 2.** Histological Characterization of Labia Minora Tissue and Vasculature. Abbreviations: H&E, Haematoxylin & Eosin; ERα, estrogen receptor-alpha; ERβ, estrogen receptor-beta; nNOS, neuronal nitric oxide; PDE3, phosphodiesterase 3; PDE4, phosphodiesterase 4; PDE5, phosphodiesterase 5; PDE11, phosphodiesterase 11.

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Author	Method	Marker	Findings
Malinovsky et al. 1975 <sup>50</sup>	Triangular resections of 5 surgical specimens and one cadaver was performed and divided into 3 parts, fixed immediately, and impregnated with silver nitrate. Evaluated 2,136 sensory nerve endings in total.	Silver nitrate	The labia minora consists of simple branched nerve endings, spray-like nerve endings, and most prominently, clew-like sensory nerve endings formed by one or more thick branching myelinated afferent axons with large nucleated Schwann cells and small nerve fibers toward the edges. They observed seven variations of the clew-like nerve endings, the most prominent being the Pacinian-like 'genital corpuscle' which contains a thick capsule. The average length of clew-like endings was reported to be 256µm with an average width of 199µm, independent of age.
Cao et al. 2021 <sup>15</sup>	Surgical and cadaveric labia minora specimen were fixed in 10% formaldehyde, embedded in paraffin, sectioned, and processed. IHC performed using the S100 antibody to identify neurons.	S-100	Abundant large myelinated sensory nerve endings in the central area of the labia minora and small, sparse, and dispersed nerve endings laterally.
Kelishadi et al. 2016 <sup>49</sup>	Four fresh tissue cadaver labia minora were analyzed. Each labia minora was divided into 6 anatomic areas and analyzed for the presence of nerve bundles using H&E and IHC for S100. Nerve density was analyzed under light microscopy, counted, and then expressed as percentage nerve density as well as number of bundles per square millimeter.	S-100	Though there is a higher trend toward overall nerve density in the superior outer and superior middle regions of the labia minora compared to inferior regions, these differences are not statistically significant, suggesting that sensory innervation may be heterogeneous throughout the labia minora.
Schober et al. 2010 <sup>52</sup>	Waste tissue strips from the surgical separation of the labial fusion of 10 2-9y/o girls were taken. Tissue was stained, fixed, frozen and cut into 30µm sections. Specimens were incubated with rabbit anti-neuronal nNOS and rabbit anti S-100 dilution 1:400. Specimen was then processed with IgG Vectastain ABC kit. Some sections were stained with Bielschowsky silver stain.	Bielschowsky silver stain	Thick nerve fibers were found in reticular and papillary dermis while thin nerve fibers were throughout the dermis and epidermis. Nerve density was reported to be most concentrated at the subepithelial plexus as well as at basal and spinous layers of the exterior epithelium. Free endings and arborizations were described with spray-like endings and seven types of clew or ball-like nerve endings as well as Pacinian corpuscles were described. Dense nerve fibers surround vascular and lymphatic plexuses.
		S-100 and nNOS	S-100 and nNOS was found more intensely and widespread at the introital border versus the exterior border as well as at the subepithelial plexus
Martin, Alguacil et al. 2011 <sup>53</sup>	Labial tissue samples were obtained following labial fusion. Immunocytochemistry against PGP 9.5, NSE, VIP, 5HTT, 5HT1A, NPY, nNOS, were performed.	PGP 9.5, NSE, VIP, 5HTT, 5HT1A, NPY, and nNOS	Pacinian-like corpuscle Inner core: 5HTT and NPY positive Outer core: PGP 9.5, 5HTT, 5HT1A, NSE External capsule: PGP 9.5, nNOS Stroma: VIP, NPY
Schober et al. 2015 <sup>5</sup>	The tissue was stained, fixed, frozen, and cut into 30µm sections. The specimens were stained by Cajal-type silver impregnation and by immunocytochemistry against protein gene product (PGP) 9.5 and neuron-specific enolase (NSE).	Cajal-type Silver staining	Free nerve endings (FNE) found in the dermis were thin, mostly tortuous, branched or single processed, straight or bent. FNEs in epidermis terminated in the stratum granulosum; dense network of free endings was identified in the strata basale and spinosum. Neither FNE in the dermis or epidermis had associated connective tissue or Schwann cells. Pacinian corpuscles, with a central structure surrounded by an encapsulated stroma, and central axon surrounded by an inner core, outer core, and external capsule, protruded into the epidermis from the dermis. There were non-capsulated or Meissner-like corpuscles were scattered in the dermal papillae and interdigitated with the epidermal ridges of the skin,
		PGP 9.5	Schwann-related cells, perineurial-related cells, and terminal axons of the non-capsulated corpuscles in the dermis were positive for PGP 9.5.
		NSE	Central axon and outer core of Pacinian corpuscles, as well as Schwann-related cells, perineurial-related cells, and terminal axons of the non-capsulated corpuscles in the dermis were positive for NSE

601 **Table 3.** Summary of results from studies on the innervation of the labia minora. Abbreviations: NSE, neuron-  
602 specific enolase; PGP 9.5, protein gene product 9.5; VIP, vasoactive intestinal peptide; NPY, neuropeptide Y;  
603 nNOS, neuronal nitric oxide.

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