

# Bölüm 24

## ADENOMYOZİS ETYOLOJİSİNDE YENİ PERSPEKTİFLER

Prof. Dr. GürkanUNCU

Adenomyozis oluşumuyla ilgili tüm güncel etyolojik hipotezleri ele alan bu bölüm özellikle fundo-kornual bölgede endomyometrial alanda doku travma ve onarımı sonrası gelişen biyolojik olayları detaylandırarak konuya ilgili bilgilerimizi güncellemekte ve yeni bilimsel çalışmalara ışık tutacak verileri okuyucu ile paylaşmaktadır. Özellikle klinik çalışmalarla zemin hazırlayacak deneysel adenomyozis modellerinden bahsedilmesi konuya ilgili yeni çalışmalarda bu modellerin kullanılmasına olanak sağlayarak hastalığın oluşum mekanizmaları ve bağlantılı olarak tedavisiyle ilgili özgün yöntemlerin gelişmesine olanak sağlayacaktır. Klinisyenlerin uterus denince, endometrium, myometrium ve serozadan ziyade archiomymometrium, subendometrial alan, slow wave uterin kasılmaları, myometrial yırtılma, mikrotravmalar ve onarımı, uterin junctional zonlar ve uterin mezenkimal kök hücre kavramlarını hatırlamaları hem hasta yönetimlerinde hem de akademik çalışmalarında farklı alanlara yönlenmelerine olanak sağlayacaktır.

### Editorial

### Giriş

Adenomyozis bilinmeyenleri bilinenlerin yanında daha fazla olan jinekolojik sorunlardan birisidir. Endometriozisden daha erken tanımlanan bir hastalık olmasına rağmen, çalışmalar endometriozis üzerinde yoğunlaşmış ve adenomyozis uzun yıllar önemsenmemiştir. Özellikle son 15 yıldır infertilite

ile olan ilişkisi bu hastalığı yeniden odak haline getirmiştir.

### Tanım ve Epidemiyolojik faktörler – prevelans

Adenomyozis basit olarak, endometrium oluşturan bez epitelii ve stroma dokusunun myometrium içinde bulunması olarak açıklanabilir. Genel olarak şimdije kadar kabul edilen görüş, endometriumun basal tabakası ile myometrium arasındaki sınırın bozulduğu ve buradan myometrium içine invazyon olduğu şeklinde olmakla birlikte, bu teoride günümüzde yeniden tartışılmaya başlanmıştır.

Prevelansı son derece tartışmalıdır. Bu tartışmanın temelinde yatan neden ise adenomyozisin tanısındaki güçlüğtür. Kesin tanı hastanın uterusunda adenomyosis odaklarının gösterilmesi ile konulur. Bu şekilde histerektomi yapılarak patoloji spesmeninde tanı konmuş adenomyozis prevalansı % 8-27 arasındadır.

Tanı genellikle 40-50'li yaşlarda konulmaktadır. Tanının bu kadar geç yaşlarda konuluyor olmasının 3 nedeni olabilir. Birincisi hastalığın ilerleyen yaşlarda ortaya çıkıyor olması, ikincisi bu yaşlarda semptomlarının artması ve hastanın doktora gitmesi üçüncüsü ise erken yaşlarda da varolan adenomyozisin tanınmasındaki güçlüklerdir. Özellikle ‘nedeni açıklanamayan infertilite’ grubundaki hastaların adenomyozis gözüyle değerlendirilmeleri bu hastalığın erken yaşlarda ve subinfertil grupta

15. Noble LS, Simpson ER, Johns A, Bulun SE. iAromatase expression in endometriosis. *J Clin Endocrinol Metab* 1996;81:174–179 37.
16. Noble LS, Takayama K, Zeitoun KM, Putman JM, Johns DA, Hinshelwood MM, Agarwal VR, Zhao Y, Carr BR, Bulun SE. Prostaglandin E2 stimulates aromatase expression in endometriosis-derived stromal cells. *J Clin Endocrinol Metab* 1997;82:600–606 38.
17. Kitawaki J, Noguchi T, Amatsu T, Maeda K, Tsukamoto K, Yamamoto T, Fushiki S, Osawa Y, Honjo H. Expression of aromatase cytochrome P450 protein and messenger ribonucleic acid in human endometriotic and adenomyotic tissues but not in normal endometrium. *Biol Reprod* 1997;57:514–519 39.
18. Hudelist G, Czerwenka K, Keckstein J, Haas C, Fink-Retter A, Gschwantler-Kaulich D, Kubista E, Singer CF. Expression of aromatase and estrogen sulfotransferase in eutopic and ectopic endometrium: evidence for unbalanced estradiol production in endometriosis. *Reprod Sci* 2007;14:798–805.
19. Aghajanova L, Hamilton A, Kwintkiewicz J, Vo KC, Giudice LC. Steroidogenic enzyme and key deciduation marker dysregulation in endometrial stromal cells from women with versus without endometriosis. *Biol Reprod* 2009;80:105–114.
20. Bulun SE. Endometriosis. *N Engl J Med* 2009;360:268–279.
21. Absenger Y, Hess-Stumpf H, Kreft B, Kratzschmar J, Haendler B, Schutze N, Regidor PA, Winterhager E. Cyr61, a deregulated gene in endometriosis. *Mol Hum Reprod* 2004;10:399–407.
22. Gashaw I, Hastings JM, Jackson KS, Winterhager E, Fazleabas AT. Induced endometriosis in the baboon (*Papio anubis*) increases the expression of the proangiogenic factor CYR61 (CCN1) in eutopic and ectopic endometria. *Biol Reprod* 2006;74:1060–1066.
23. Leyendecker G, Kunz G, Noe M, Herbertz M, Mall G. Endometriosis: a dysfunction and disease of the archimetra. *Hum Reprod Update* 1998;4:752–762.
24. Leyendecker G, Kunz G, Wildt L, Beil D, Deininger H. Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility. *Hum Reprod* 1996;11:1542–1551.
25. Kunz G, Noe M, Herbertz M, Leyendecker G. Uterine peristalsis during the follicular phase of the menstrual cycle. Effects of oestrogen, anti-oestrogen and oxytocin. *Hum Reprod Update* 1998;4:647–654.
26. Moen MH, Muus KM. Endometriosis in pregnant and non-pregnant women at tubal sterilisation. *Hum Reprod* 1991;6:699–702.
27. Kunz G, Beil D, Huppert P, Noe M, Kissler S, Leyendecker G. Adenomyosis in endometriosis—prevalence and impact on fertility. Evidence from magnetic resonance imaging. *Hum Reprod* 2005;20:2309–2316.
28. Leyendecker G. Endometriosis is an entity with extreme pleiomorphism. *Hum Reprod* 2000;15:4–7.
29. Zervomanolakis I, Ott HW, Müller J, Seeber BE, Friess SC, Mattle V, Virgolini I, Heute D, Wildt L. Uterine mechanisms of ipsilateral directed spermatozoa transport: evidence for a contribution of the utero-ovarian countercurrent system. *Eur J Obstet Gynecol Reprod Biol* 2009;144(Suppl 1):S45–S49.
30. Ashcroft GS, Ashworth JJ. Potential role of estrogens in wound healing. *Am J Clin Dermatol* 2003;4:737–743.
31. Gilliver SC, Ashworth JJ, Ashcroft GS. The hormonal regulation of cutaneous wound healing. *Clin Dermatol* 2007;25:56–62.
32. Mowa CN, Hoch R, Montavon CL, Jesmin S, Hindman G, Hou G. Estrogen enhances wound healing in the penis of rats. *Biomed Res* 2008;29:267–270.
33. Yang G, Im HJ, Wang JH. Repetitive mechanical stretching modulates IL-1beta induced COX-2, MMP-1 expression, and PGE2 production in human patellar tendon fibroblasts. *Gene* 2005;363:166–172.
34. Hadjiafragiou M, Ahrens W, Rubin CT. Temporal expression of the chondrogenic and angiogenic growth factor CYR61 during fracture repair. *J Bone Miner Res* 2000;15:1014–1023.
35. Garcia-Segura LM, Wozniak A, Azcoitia I, Rodriguez JR, Hutchison RE, Hutchison AB. Aromatase expression by astrocytes after brain injury: implications for local estrogen formation in brain repair. *Neuroscience* 1999;89:567–578.
36. Kunz G, Herbertz M, Noe M, Leyendecker G. Sonographic evidence of a direct impact of the ovarian dominant structure on uterine function during the menstrual cycle. *Hum Reprod Update* 1998;4:667–672.
37. Kunz G, Beil D, Deininger H, Wildt L, Leyendecker G. The dynamics of rapid sperm transport through the female genital tract. Evidence from vaginal sonography of uterine peristalsis (VSUP) and hysterosalpingoscinigraphy (HSSG). *Hum Reprod* 1996;11:627–632.
38. Yang G, Im HJ, Wang JH. Repetitive mechanical stretching modulates IL-1beta induced COX-2, MMP-1 expression, and PGE2 production in human patellar tendon fibroblasts. *Gene* 2005;363:166–172.
39. Harada M, Osuga Y, Hirota Y, Koga K, Morimoto C, Hirata T, Yoshino O, Tsutsumi O, Yano T, Taketani Y. Mechanical stretch stimulates interleukin-8 production in endometrial stromal cells: possible implications in endometrium-related events. *J Clin Endocrinol Metab* 2005;90(2):1144–1148.
40. Hadweld RM, Yudkin PL, Coe CL, ScheZer J, Uno H, Barlow DH, Kemnitz JW, Kennedy SH. Risk factors for endometriosis in the rhesus monkey (*Macaca mulatta*): a case-control study. *Hum Reprod Update* 1997;3:109–115.
41. Zingg HH, Rosen F, Chu K, Larcher A, Arslan AM, Richard S, Lefebvre D. Oxytocin and oxytocin receptor gene expression in the uterus. *Recent Progr Hormone Res* 1995;50:255–273.
42. Mitzumoto Y, Furuya K, Makimura N, Mitsui C, Seki K, Kimura T, Nagata I. Gene expression of oxytocin receptor in human eutopic endometrial tissues. *Adv Exp Med Biol* 1995;395:491–493.
43. Fusi L, Cloke B, Brosen J. The uterine junctional zone. *Best Pract Res Clin Obstet Gynaecol* 2006;20:479–491.

44. Fleischer AC, Mendelson EB, Bohm-Velez M et al. Transvaginal and transabdominal sonography of the endometrium. *Semin Ultrasound CT MR* 1988; 9: 81e101.
45. KunzG, BeilD, Huppert P. Structural abnormalities of the uterine wall in women with endometriosis and infertility visualized by vaginal sonography and magnetic resonance imaging. *Hum Reprod* 2000; 15: 76-82.
46. McCarthy S, Scott G, Majumdar S et al. Uterine junctional zone: MR study of water content and relaxation properties. *Radiology* 1989; 171: 241-243.
47. Scrott LM, Flynn SD, Luthringer DJ et al. Junctional zone of the uterus: correlation of MR imaging and histologic examination of hysterectomy specimens. *Radiology* 1991; 179: 403-407.
48. Xu S, Yang Y, Gregory CD et al. Biochemical heterogeneity in hysterectomized uterus measured by 31P NMR using SLIM localization. *Magn Reson Med* 1997; 37: 736-743.
49. Brosens JJ, de Souza NM, Barker FG. Uterine junctional zone: function and disease. *Lancet* 1995; 346: 558-560.
50. Tetlow RL, Richmond I, Manton DJ et al. Histological analysis of the uterine junctional zone as seen by transvaginal ultrasound. *Ultrasound Obstet Gynecol* 1999; 14: 188-193.
51. Koff AK. Development of the vagina in the human fetus. *Contrib Embryol* 1933; 24: 59-91.
52. O'Rahilly R. Prenatal human development. In Wynn R (ed.). *Biology of the Uterus*. New York: Plenum Press; 1977, pp. 35-57.
53. Daels J. Uterine contractility patterns of the outer and inner zones of the myometrium. *Obstet Gynecol* 1974; 44: 315-326.
54. Brosens JJ, Barker FG , de Souza NM. Myometrial zonal differentiation and uterine junctional zone hyperplasia in the non-pregnant uterus. *Hum Reprod Update* 1998; 4: 496-502.
55. Noe M, Kunz G, Herbertz M et al. The cyclic pattern of the immunocytochemical expression of oestrogen and progesterone receptors in human myometrial and endometrial layers: characterization of the endometrial-subendometrial unit. *Hum Reprod* 1999; 14: 190-197.
56. Fujii S, Konishi I, Mori T. Smooth muscle differentiation at endometrio-myometrial junction. An ultra-structural study. *Virchows Arch A Pathol Anat Histopathol* 1989; 414: 105-112.
57. Glatstein IZ, Yeh J. Ontogeny of the estrogen receptor in the human fetal uterus. *J Clin Endocrinol Metab* 1995; 80: 958-964.
58. McCarthy S, Tauber C, Gore J. Female pelvic anatomy: MR assessment of variations during the menstrual cycle and with use of oral contraceptives. *Radiology* 1986; 160: 119-123.
59. Demas BE, Hricak H, Jaffe RB. Uterine MR imaging: effects of hormonal stimulation. *Radiology* 1986; 159: 123-126.
60. Janus CL, Wiczyk HP, Laufer N. Magnetic resonance imaging of the menstrual cycle. *Magn Reson Imaging* 1988; 6: 669-674.
61. Wiczyk HP, Janus CL, Richards CJ et al. Comparison of magnetic resonance imaging and ultrasound in evaluating follicular and endometrial development throughout the normal cycle. *Fertil Steril* 1988; 49: 969-972.
62. Turnbull LW, Manton DJ, Horsman A et al. Magnetic resonance imaging changes in uterine zonal anatomy during a conception cycle. *Br J Obstet Gynaecol* 1995; 102: 330-331.
63. Barton JW, McCarthy SM, Kohorn EI et al. Pelvic MR imaging findings in gestational trophoblastic disease, incomplete abortion, and ectopic pregnancy: are they specific? *Radiology* 1993; 186: 163-168.
64. de Vries K, Lyons EA, Ballard G et al. Contractions of the inner third of the myometrium. *Am J Obstet Gynecol* 1990; 162: 679-682.
65. Lyons EA, Taylor PJ, Zheng XH et al. Characterization of subendometrial myometrial contractions throughout the menstrual cycle in normal fertile women. *Fertil Steril* 1991; 55: 771e774.
66. Kunz G. Uterine peristalsis throughout the menstrual cycle: physiological and pathophysiological aspects. *Hum Reprod Update (CD-ROM)*; 1996; 2.
67. Ijland MM, Evers JL, Dunselman GA et al. Endometrial wavelike movements during the menstrual cycle. *Fertil Steril* 1996; 65: 746-749.
68. Ivers JL, Hoogland HJ. Velocity of endometrial wavelike activity in spontaneous cycles. *Fertil Steril* 1997; 68: 72-75.
69. Ijland MM, Evers JL, Dunselman GA et al. Relation between endometrial wavelike activity and fecundability in spontaneous cycles. *Fertil Steril* 1997; 67: 492-496.
70. Kunz G, Beil D, Deininger H et al. The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. *Hum Reprod* 1996; 11: 627-632.
71. Kido A, Togashi K, Nakai A et al. Oral contraceptives and uterine peristalsis: evaluation with MRI. *J Magn Reson Imaging* 2005; 22: 265-270.
72. Lesny P, Killick SR, Tetlow RL et al. Uterine junctional zone contractions during assisted reproduction cycles. *Hum Reprod Update* 1998; 4: 440-445.
73. Fanchin R, Righini C, Olivennes F et al. Uterine contractions at the time of embryo transfer alter pregnancy rates after in-vitro fertilization. *Hum Reprod* 1998; 13: 1968-1974.
74. Lesny P & Killick SR. The junctional zone of the uterus and its contractions. *BJOG* 2004; 111: 1182-1189.
75. Mansour RT, Aboulghar MA, Serour GI et al. Dummy embryo transfer using methylene blue dye. *Hum Reprod* 1994; 9: 1257-1259.
76. Knutzen V, Stratton CJ, Sher G et al. Mock embryo transfer in early luteal phase, the cycle before in vitro fertilization and embryo transfer: a descriptive study. *Fertil Steril* 1992; 57: 156-162.
77. Stewart CJ, Farquharson MA, Foulis AK. The distribution and possible function of gamma interferon- immunoreactive cells in normal endometrium and myo-

- metrium. *Virchows Arch A Pathol Anat Histopathol* 1992; 420: 419-424.
78. Tabibzadeh SS, Satyaswaroop PG, Rao PN. Antiproliferative effect of interferon-gamma in human endometrial epithelial cells in vitro: potential local growth modulatory role in endometrium. *J Clin Endocrinol Metab* 1988; 67: 131-138.
  79. Tabibzadeh S, Sun XZ, Kong QF et al. Induction of a polarized micro-environment by human T cells and interferon-gamma in three-dimensional spheroid cultures of human endometrial epithelial cells. *Hum Reprod* 1993; 8: 182-192.
  80. Mori A, Zhai YL, Toki T et al. Distribution and heterogeneity of mast cells in the human uterus. *Hum Reprod* 1997; 12: 368-372.
  81. Mori A, Nakayama K, Suzuki J et al. Analysis of stem cell factor for mast cell proliferation in the human myometrium. *Mol Hum Reprod* 1997; 3: 411-418.
  82. Galli SJ. New concepts about the mast cell. *N Engl J Med* 1993; 328: 257-265.
  83. Yeaman GR, Guyre PM, Fanger MW et al. Unique CD8<sup>b</sup> T cell-rich lymphoid aggregates in human uterine endometrium. *J Leukoc Biol* 1997; 61: 427-435.
  84. Piersanti M, Lye SJ. Increase in messenger ribonucleic acid encoding the myometrial gap junction protein, connexin-43, requires protein synthesis and is associated with increased expression of the activator protein-1, c-fos. *Endocrinology* 1995; 136: 3571-3578.
  85. Geimonen E, Jiang W, Ali M et al. Activation of protein kinase C in human uterine smooth muscle induces connexin-43 gene transcription through an AP-1 site in the promoter sequence. *J Biol Chem* 1996; 271: 23667-23674.
  86. Webb P, Lopez GN, Uht RM et al. Tamoxifen activation of the estrogen receptor/AP-1 pathway: potential origin for the cell-specific estrogen-like effects of antiestrogens. *Mol Endocrinol* 1995; 9: 443-456.
  87. Zhao K, Kuperman L, Geimonen E et al. Progestin represses human connexin43 gene expression similarly in primary cultures of myometrial and uterine leiomyoma cells. *Biol Reprod* 1996; 54: 607-615.
  88. Cameron IT, Davenport AP, van Papendorp C et al. Endothelin-like immunoreactivity in human endometrium. *J Reprod Fertil* 1992; 95: 623-628.
  89. Bacon CR, Morrison JJ, O'Reilly G et al. ETA and ETB endothelin receptors in human myometrium characterized by the subtype selective ligands BQ123, BQ3020, FR139317 and PD151242. *J Endocrinol* 1995; 144: 127-134.
  90. Figueira PG, Abrao MS, Krikun D, Taylor H. Stem cells in endometrium and their role in the pathogenesis of endometriosis. *Ann NY Acad Sci*. 2001;1221:10-17
  91. Patel AN, Park E, Kuzman M, Benetti F, Silva FJ, Allickson JG. Multipotent menstrual blood stromal stem cells: isolation, characterization, and differentiation. *Cell Transplant*. 2008;17:303-311.
  92. Gargett CE, Masuda H. Adult stem cells in the endometrium. *Mol Hum Reprod*. 2010; 16:818- 834.
  93. Chan RW, Schwab KE, Gargett CE. Clonogenicity of human endometrial epithelial and stromal cells. *Biol Reprod*. 2004; 70:1738-1750.
  94. Schwab KE, Chan RW, Gargett CE. Putative stem cell activity of human endometrial epithelial and stromal cells during the menstrual cycle. *Fertil Steril*. 2005; 84(Suppl 2):1124-1130.
  95. Tai MH, Chang CC, Kiupel M, Webster JD, Olson LK, Trosko JE. Oct4 expression in adult human stem cells: evidence in support of the stem cell theory of carcinogenesis. *Carcinogenesis*. 2005; 26:495-502.
  96. Matthai C, Horvat R, Noe M, Nagele F, Radjabi A, van Trotsenburg M, Huber J, Kolbus A. Oct-4 expression in human endometrium. *Mol Hum Reprod*. 2006; 12:7-10.
  97. Bentz EK, Kenning M, Schneeberger C, Kolbus A, Huber JC, Hefler LA, Tempfer CB. OCT-4 expression in follicular and luteal phase endometrium: a pilot study. *Reprod Biol Endocrinol*. 2010; 8:38.
  98. Cho NH, Park YK, Kim YT, Yang H, Kim SK. Lifetime expression of stem cell markers in the uterine endometrium. *Fertil Steril*. 2004; 81:403-407.
  99. Lynch L, Golden-Mason L, Egan M, O'Herlihy C, O'Farrelly C. Cells with haematopoietic stem cell phenotype in adult human endometrium: relevance to infertility? *Hum Reprod*. 2007; 22:919- 926
  100. Gotte M, Wolf M, Staebler A, Buchweitz O, Kelsch R, Schuring AN, Kiesel L. Increased expression of the adult stem cell marker Musashi-1 in endometriosis and endometrial carcinoma. *J Pathol*. 2008; 215:317-329.
  101. Gargett CE, Masuda H. Adult stem cells in the endometrium. *Mol Hum Reprod* 2010;16:818-834.
  102. Starzinski-Powitz A, Zeitvogel A, Schreiner A, Baumann R. In search of pathogenic mechanisms in endometriosis: the challenge for molecular cell biology. *Curr Mol Med* 2001;1:655-664.
  103. Leyendecker G, Herbertz M, Kunz G, Mall G. Endometriosis results from the dislocation of basal endometrium. *Hum Reprod* 2002; 17:2725 – 2736.
  104. Gargett CE. Identification and characterisation of human endometrial stem/progenitor cells. *Aust N Z J Obstet Gynaecol* 2006;46:250–253.
  105. Gargett CE. Uterine stem cells: what is the evidence? *Hum Reprod Update* 2007;13:87-101.
  106. Sasson IE, Taylor HS. Stem cells and the pathogenesis of endometriosis. *Ann NY Acad Sci* 2008;1127:106-115.
  107. Masuda H, Kalka C, Takahashi T, Yoshida M, Wada M, Kobori M, Itoh R, Iwaguro H, Eguchi M, Iwami Y et al. Estrogen-mediated endothelial progenitor cell biology and kinetics for physiological postnatal vasculogenesis. *Circ Res* 2007a;101:598–606.
  108. Bokor A, Debrock S, Drijkoningen M, Goossens W, Fulop V, 'Hooghe T. Quantity and quality of retrograde menstruation: a case control study. *Reprod Biol Endocrinol* 2009;7:123.
  109. Gargett CE, Guo SW. Stem cells and clonality in endometriosis. In: Garcia-Velasco J, Rizk B (eds). *Endometriosis: Current Management and Future Trends*. New Delhi: Jaypee Brothers Medical Publishers, 2010, 308–317.

110. Masuda H, Maruyama T, Hiratsu E, Yamane J, Iwanami A, Nagashima T, Ono M, Miyoshi H, Okano HJ, Ito M et al. Noninvasive and real-time assessment of reconstructed functional human endometrium in NOD/SCID/gnc<sup>ull</sup> immunodeficient mice. *Proc Natl Acad Sci USA* 2007; 104: 1925 – 1930.
111. Schwab KE, Gargett CE. Co-expression of two perivascular cell markers isolates mesenchymal stem-like cells from human endometrium. *Hum Reprod* 2007; 22: 2903–2911.
112. Tosh D, Slack JMW. How cells change their phenotype. *Nat Rev Mol Cell Biol* 2002; 3: 187–194.
113. Taylor HS. Endometrial cells derived from donor stem cells in bone marrow transplant recipients. *J Am Med Assoc* 2004; 292: 81–85.
114. Chen YJ, Li HY, Chang YL, Yuan CC, Tai LK, Lu KH, Chang CM, Chiou SH. Suppression of migratory/invasive ability and induction of apoptosis in adenomyosis-derived mesenchymal stem cells by cyclooxygenase-2 inhibitors. *Fertil Steril* 2010;
115. Greaves P. Experimental adenomyosis. *Best Pract Res Clin Obstet Gynaecol* 2006; 20: 503–510.
116. DiGiacomo RF. Gynecologic pathology in the rhesus monkey (*Macaca mulatta*). II. Findings in laboratory and free-ranging monkeys. *Vet Pathol* 1977; 14: 539–546.
117. Baskin GB, Smith SM & Marx PA. Endometrial hyperplasia, polyps, and adenomyosis associated with unopposed estrogen in rhesus monkeys (*Macaca mulatta*). *Vet Pathol* 2002; 39: 572–575.
118. Stocklin-Gautschi NM, Gusetti F, Reichler IM et al. Identification of focal adenomyosis as a uterine lesion in two dogs. *J Small Anim Pract* 2001; 42: 413–416.
119. Gelberg HB & McEntee K. Pathology of the canine and feline uterine tube. *Vet Pathol* 1986; 23: 770–775.
120. Kida H. Histological analysis of spontaneous adenomyosis-like changes in recombinant inbred mouse uterus (SMXA mouse) - a novel animal model for adenomyosis. *Acta Obstet Gynaecol Jpn* 1994; 46: 323–330.
121. Mori T, Singtripop T & Kawishawa S. Animal model of uterine adenomyosis: Is prolactin a potent inducer of adenomyosis in mice? *Am J Obstet Gynecol* 1991; 165: 232–234.
122. Huseby RA & Thurlow S. Effects of prenatal exposure of mice to “low dose” diethylstilbestrol and the development of adenomyosis associated with evidence of hyperprolactinemia. *Am J Obstet Gynecol* 1982; 144: 939–949.
123. Lacassagne A. Modifications progressives de l’utérus de la souris sous l’action prolongée de l’œstrone. *C R Soc Biol* 1935.
124. Guttner J. Adenomyosis in mice. *Z Versuchstierkd* 1980; 22: 249–251.
125. Ostrander PL, Mills KT & Bern HA. Long-term responses of the mouse uterus to neonatal diethylstilbestrol treatment and to later sex hormone exposure. *J Natl Cancer Inst* 1985; 74: 121–135.
126. Lipschutz A, Iglesias R, Panasevich VI et al. Pathological changes induced in the uterus of mice with the prolonged administration of progesterone and 19-nor-contraceptives. *Br J Cancer* 1967; 21: 160–165.
127. Mori T & Nagasawa H. Mechanisms of development of prolactin-induced adenomyosis in mice. *Acta Anatomica* 1983; 116: 46–54.
128. Matsuda M, Sesabe H, Adachi Y et al. Increased invasion activity of endometrial stromal cells and elevated expression of matrix metalloproteinase messenger RNA in the uterine tissues of mice with experimentally induced adenomyosis. *Am J Obstet Gynecol* 2001; 185: 1374–1380.
129. Zhou YF, Mori T, Nagasawa H et al. Probucol, a hypocholesterolemic agent, prevents the development of uterine adenomyosis induced by pituitary grafting in mice. *Anticancer Res* 2004; 24: 2209–2212.
130. Yamashita M, Matsuda M & Mori T. In situ detection of prolactin receptor mRNA and apoptotic cell death in mouse uterine tissues with adenomyosis. *In Vivo* 1999; 13: 57–60.
131. Mori T, Nagasawa H & Takahashi S. The induction of adenomyosis in mice by intrauterine pituitary isografts. *Life Sci* 1981; 29: 1277–1282.
132. Zhou YF, Matsuda M, Sakamoto S et al. Changes in uterine microvessels as a possible pathogenic factor in the development of adenomyosis induced by pituitary grafting in mice. *Acta Histochem Cytochem* 1999; 32: 387–391.
133. Schneider JE, Berk BC, Gravanis MB et al. Probucol decreases neointimal formation in a swine model of coronary artery balloon injury: a possible role for antioxidants in restenosis. *Circulation* 1993; 88: 628–637.
134. Parrott E, Butterworth M, Green A et al. Adenomyosis - a result of disordered stromal differentiation. *Am J Pathol* 2001; 159: 623–630.
135. Gray D, Greaves P, Styles J et al. Pathology and gene expression changes in the uteri of mice dosed with estradiol or tamoxifen. *Toxicology* 2004; 202: 114–115.
136. Green AR, Styles JA, Parrott E et al. The role of nerve growth factor in the development of adenomyosis in CD-1 mice caused by tamoxifen. *Toxicology* 2004; 194: 264–265.
137. Meissner WA, Sommers SC & Sherman G. Endometrial hyperplasia, endometrial carcinoma, and endometriosis produced experimentally by estrogen. *Cancer* 1957; 10: 500–509.