Chapter 6
The Genetic-Epigenetic Pathophysiology of Endometriosis: A Surgeon's View

Philippe R. Koninckx, Anastasia Ussia, Leila Adamyan, Jörg Keckstein, Arnaud Wattiez, Victor Gomel, and Dan C. Martin

P. R. Koninckx (✉)
Latiffa Hospital, Dubai, United Arab Emirates

Gruppo Italo Belga, Villa Del Rosario Rome, Italy

Professor emeritus OBGYN, KU Leuven, Leuven, Belgium

Prof Em. University of Oxford-Hon Consultant, Oxford, UK

Prof em. University Cattolica del Sacro Cuore, Roma, Italy

Hon Professor, Moscow State University, Moscow, Russia

A. Ussia
Gruppo Italo Belga, Villa Del Rosario Rome, Italy

Consultant Università Cattolica, Gemelli hospitals, Roma, Italy

L. Adamyan
Department of Operative Gynecology, Federal State Budget Institution V. I. Kulakov Research Centre for Obstetrics, Gynecology, and Perinatology, Ministry of Health of the Russian Federation, Moscow, Russia

Department of Reproductive Medicine and Surgery, Moscow State University of Medicine and Dentistry, Moscow, Russia

J. Keckstein
Endometriosis Centre, Dres. Keckstein, Villach, Austria

University Ulm, Ulm, Germany
e-mail: joerg@keckstein.at

A. Wattiez
Latiffa Hospital, Dubai, United Arab Emirates

Department of obstetrics and gynaecology, University of Strasbourg, Strasbourg, France

V. Gomel
Professor emeritus Department of Obstetrics and Gynecology, University of British Columbia and Women's Hospital, Vancouver, BC, Canada

D. C. Martin
Professor emeritus School of Medicine, University of Tennessee Health Science Centre, Memphis, TN, USA

Institutional Review Board, Virginia Commonwealth University, Richmond, VA, USA

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Introduction

In the absence of a clear understanding of the pathophysiology, endometriosis remains a poorly understood disease. A major problem is the absence of an animal model with enough similarity to the human myometrium, junctional zone (JZ), endometrium, placentation, and pregnancy disorders as preeclampsia. Prevention, diagnosis, and therapy are based on observational medicine and clinical experience. Without experimentation and without understanding the pathophysiology, our views on endometriosis are limited to clinical observations, histology, and biochemical investigations of endometriotic tissues.

The history of our understanding of the pathophysiology of endometriosis will be reviewed together with the recent genetic-epigenetic theory [1]. In order to understand these concepts on endometriosis, it is important to realize how our knowledge varied over time.

The History of Endometriosis

The early history of endometriosis, discussed at length in Chap. 2, is linked to the development of microscopy and histology. Only in the mid-nineteenth century, compound microscopes had acquired sufficient magnification, which together with tissue fixation and embedding techniques permitted the study of histologic structures. Modern histology started only at the end of the century after the development of a microtome. Rokitanski [2] is often credited with the first description of endometrium-like tissue in 1860. However, he (Fig. 6.1) described endometrial


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Fig. 6.1 The original article of Rokitansky

polyps and an ovarian cancer with endometrium-like cells. Descriptions of what today would be called deep endometriosis were made at the end of the nineteenth [3–5] and during the early twentieth [6–10] century. Slightly later, cystic ovarian endometriosis was described by Sampson [11, 12] who coined the name "endometriosis" [13, 14] and proposed the retrograde menstruation and implantation theory [11]. Over the next 50 years, numerous reports described "endometrium like tissue outside the uterus" found in all kind of surgery specimens. Aleady in 1960 [15], it was realized that endometriosis was a frequent finding in women undergoing surgery even after menopause.

Only after the introduction of diagnostic laparoscopy it was realized that black-puckered, "powder burn," superficial peritoneal lesions in sclerotic areas, later called typical lesions, were very frequent in women with pain and/or infertility. When in 1980 [16, 17] we realized that retrograde menstruation occurred almost systematically in all women, the search for early lesions after implantation started. Although occasionally described before [12, 18–22], the high prevalence of subtle lesions [23, 24] was only realized after 1986 [25]. Also, microscopic endometriosis [26, 27] turned out to be a frequent finding even in normal-looking peritoneum [28] and much later in lymphoid glands [29, 30] and in the bowel at distance from deep endometriosis [31]. With the introduction of transvaginal ultrasound, cystic ovarian endometriosis became a frequent finding. With the introduction of excisional laparoscopic surgery, some endometriosis lesions were found to infiltrate deeper under the peritoneal surface [32], and deep endometriosis became recognized as a frequent entity of endometriosis associated with severe pain, invasion into the muscle of the bowel wall, occasional nerve invasion [33], and a neurotropic effect [34, 35].

The Definition of Endometriosis and the Natural History

From the very beginning till today, the definition of endometriosis has been "endometrium like glands and stroma outside the uterus" diagnosed on histologic slides after routine staining. It is surprising that other staining techniques and histochemistry did not add to the diagnosis of endometriosis. Histology after routine staining thus remained the gold standard. A consequence of this definition is that all observations not fitting this histological definition are not recognized as endometriosis. This comprises Müllerianosis [36], stromatosis [37], and eventual atypical or precursor lesions. Also, vascularization and fibrosis are not included in the diagnosis.

The histology of endometriosis lesions seems well established. Subtle lesions have active glands and stroma, and typical lesions are generally burnt out. The endometrial component of cystic ovarian endometriosis varies from hemosiderin-laden macrophages only to inactive endometrial glands and stroma to occasional proliferative endometrium-like tissue. Deep endometriosis consists of fibro-muscular tissue with sparse glands and stroma which can be active in the deeper parts. It is important to realize that histology does not permit a clear distinction between typical and deep endometriosis. The distinction is surgical.

That larger cystic ovarian endometriosis and larger deep endometriosis lesions were a clinical pathology requiring surgery, was recognized from the beginning. However, it is much less clear whether all microscopic, subtle, typical, smaller cystic, and deep endometriosis lesions are a clinical pathology. This is not surprising since histological diagnosis requires excision.

For the same reason, the natural history of the disease is poorly known, and the concept that endometriosis is a progressive disease, although logic, is poorly documented [38]. Regression of smaller (subtle) lesions is common [39]. Rectovaginal deep endometriosis lesions without pain do not grow rapidly [40]. Also, the concept that endometriosis is a recurrent disease is mainly based on the frequently observed retrograde menstruation and the concept of implantation [41]. The available data do not permit to distinguish between recurrence because of incomplete surgery and the formation of new lesions. Moreover, studies rather describe recurrence of symptoms than recurrence of lesions [42]. Recurrence rates of cystic ovarian endometriosis following stripping are less than 10% within 6 months [43, 44] but vary with the surgeon [45] and with the technique used. Recurrence rates of deep endometriosis lesions after excision are rare (personal observations and [42]). The recurrence rates of typical lesions and subtle lesions are believed to be higher although the data are limited.

Observations and Associated Pathologies

Endometriosis occasionally occurs in women without an endometrium [46, 47] and in men [48, 49]. The epidemiology is unclear since diagnosis often requires a laparoscopy and since recognition varies with the expertise of the surgeon. This limits the information of hospital-based discharge records [50]. Subtle endometriosis lesions decrease with age, whereas typical, cystic, and deep lesions increase with age [51]. Clinical observation suggests that the prevalence and severity of deep endometriosis are increasing [40].

Endometriosis is *associated with pain and infertility* (Table 6.1). However, it is unclear whether microscopic and subtle endometriosis [31] commonly cause pain or infertility given the high prevalence in women with infertility with no pain [51]. Typical endometriosis is estimated to cause minor pain in 50% of women. Half of them are pain-free as estimated in women with infertility only [51]. However, analysis of pain is compromised as symptoms may not lead to a diagnosis in the 62% of women whose symptoms are only found on direct questioning [52, 53] or in those with no symptoms but with endometriosis found at tubal ligation [54]. Cystic ovarian endometriosis causes pain in over 80%, and deep endometriosis causes severe pain in the large majority of women [51]. Following surgical excision of endometriosis and after failed IVF and of deep endometriosis, 50% [55] and 30–50% [56] will conceive spontaneously, respectively. The mechanism of the associated infertility is unknown. That cystic ovarian endometriosis is a cause of infertility can be explained by the associated adhesions.

Table 6.1 Clinical observations in endometriosis

Clinical observations on endometriosis
1. Variable appearance (subtle-typical-cystic-deep)
2. Occurs also in women without endometrium and in men
3. An hereditary disease and predisposition
4. Natural history Most subtle lesions do not progress Most typical-cystic-deep lesions are not progressive after diagnosis Most typical-cystic-deep lesions are not recurrent after surgery
5. Epidemiology of endometriosis
6. An heterogeneous disease
7. Endometriosis is associated with Pain and infertility Adenomyosis Changes in plasma Changes in peritoneal fluid Changes in endometrium Changes in pregnancy outcome Pelvic infections Cancer risk Total body radiation and dioxin intake
The endometriosis lesion
8. Clonal
9. Altered biology: estrogen production – progesterone resistance, etc.

Reproduced with permission from [1]

Endometriosis is *associated with adenomyosis* [57]. Focal adenomyotic nodules are associated with deep endometriosis [58, 59]. Endometriosis is associated with *changes in plasma* as immunology [60–62], lymphocytes [63], prostaglandins [64], insulin-like growth factor I [65], and a decreased natural killer cell (NK) activity. *Changes in peritoneal fluid* are the luteinized unruptured follicle syndrome, with much lower concentrations of estrogens and progesterone after ovulation [66]; the low-grade inflammation with a high number of activated macrophages [67] and changes in cytokines [68, 69]; growth factors, acylcarnitines, phosphatidylcholines, and sphingomyelins [70]; vascular epithelial growth factor [71, 72]; and other angiogenic factors [73, 74] especially of the TGFb superfamily [75]; and increased concentrations of CA125 and of glycodelins [76]. Several hundred minor biochemical *changes in the endometrium* have been described [77, 78]. *Contractility of the uterus* is modified in women with deep endometriosis or adenomyosis [79]. *Changes in pregnancy,* mainly associated with cystic ovarian and deep endometriosis [80], and with adenomyosis [81], are abnormal placentation, insufficient physiologic changes in the spiral arteries, an increased risk of preterm birth, small for gestational age (SGA) babies, and preeclampsia [80]. Endometriosis is associated with a higher risk of vaginal [82], uterine [83], and pelvic *infections* [84]. Endometriosis seems associated with a higher *risk of cancer* [85, 86] [87], although the association with ovarian cancer remains debated [88] and with *dioxin* [89, 90] and *total body radiation* [91, 92].

Endometriosis is *a hereditary disease* with a 6–9% [93] and a 15% [94] increased risk of developing endometriosis in first-degree relatives of women with mild and severe endometriosis, respectively. This, together with the familial clustering in humans [95] and primates [96] and the prevalence [97] and the age of onset [98] in twin sisters, permitted the conclusion that hereditary factors accounted for 50% of endometriosis [99, 100]. The molecular mechanisms involved are not yet understood [101]. Genome-wide scanning and linkage analysis did not identify the genes involved [102]. The two loci found by linkage analysis have low LOD (logarithm of odds) scores. The 10 [103] or 15 [104] loci found by genome-wide association studies in women with severe endometriosis were located in DNA sequences regulating target genes [105]. A meta-analysis found 5 loci regulating sex steroid hormone pathways, 5 secondary signals, and 19 single nucleotide polymorphisms [106]. The investigation of specific hereditary predisposition factors as detoxication enzymes was negative [107].

Endometriosis Lesions Are Clonal with an Altered Biology Clonality was demonstrated for typical [108], deep [109], and cystic ovarian [110–112] endometriosis. Multiple lesions in one woman derive from different progenitor cells [108]. Investigation of larger endometriosis lesions [113–115] found aromatase activity [113] and progesterone resistance [114–116] together with numerous other biochemical changes [117–123]. These changes are increasingly viewed as a consequence of genetic or epigenetic polymorphism [113, 124]. Other epigenetic changes [125–127] comprise methylation, demethylation of DNA, and modifications in histone code [125, 128].

The Theories of Pathophysiology

A theory remains valid until disproven by new observations.

The Sampson Theory and the Metaplasia Theory

When formulated 100 years ago, the implantation theory [11, 13, 18] after retrograde menstruation or after lymphatic or blood embolism was logic. This theory became even more attractive when retrograde menstruation was found to be rather the rule than the exception. Retrograde menstruation contains living cells [129] with implantation and growth potential of cells [130, 131] and tissue blocks [131] as observed directy by the implantation of endometrial fragments in a neonate [132]. That pelvic endometriosis is more frequently found on the left side of the pelvis [133] and on the right side of the diaphragm seems consistent with gravity and with the clockwise circulation of peritoneal fluid. Also, the frequent finding of subtle lesions seemed consistent with this hypothesis. If considered like endometrium, it is

logical that endometriosis is estrogen and progesterone responsive, that active endometriosis does not occur after menopause, that endometriosis symptoms disappear during pregnancy, and that ovarian suppression is an effective medical therapy. The associated changes were explained as consequences of the endometriosis developing in an abnormal location. Neonatal menstruation [134–136], occurring especially in postmature and SGA babies, might explain premenarcheal and severe adolescent [137] endometriosis.

A weakness of the hypothesis was that it could not explain why subtle lesions developed into endometriosis in some women only, and why some developed into typical, cystic, or deep endometriosis. The hereditary character of endometriosis is difficult to explain, but not incompatible.

The implantation theory does not explain the clonal aspect of endometriosis lesions, many of the biochemical changes in the endometriosis tissue, and the rare active deep endometriosis more than 10 years after menopause [138]. Moreover, it is incompatible with the observation of endometriosis in women without an endometrium and in men.

The occurrence of endometriosis in women with a Rokitansky syndrome was realized already a few years after Sampson formulated his implantation theory, and therefore, the metaplasia theory was formulated [47]. After this, both theories which were otherwise similar survived side by side. The metaplasia theory was recently updated with a development from stem cells, either peritoneal [139–143] or uterine [144, 145], from bone marrow cells [140, 146–149], pale cells [150, 151], and embryonic remnants [152]. These concepts find support in the frequent mesothelial-mesenchymal transitions (MMT) with a role of platelets [153] and in the role of bone marrow cells in peritoneal repair [154].

Another variant was the archimetra theory emphasizing enhanced or abnormal uterine contractions as a cause of trauma in the endometrial-myometrial JZ [150] and of endometrial cell seeding [155].

The Endometriotic Disease and the Genetic-Epigenetic Theory

The endometriotic disease theory postulated in 1999 [156] that subtle lesions consisted of normal endometrial cells, occurring intermittently in all women [157], and that a genomic incident was required before these cells developed into typical, cystic, or deep endometriosis. In order to emphasize this difference between normal and abnormal cells, it was suggested to call them endometriosis and endometriotic disease.

The genetic-epigenetic theory (Fig. 6.2) updates the endometriotic disease theory [1]. All humans are born with a specific set of minor genetic and epigenetic (G-E) incidents transmitted by the parents or acquired in utero (Fig. 6.3). This can explain the heredity predisposition of endometriosis and most endometriosis-associated changes in plasma, immunology, peritoneal fluid, and even the infertility. They can also explain changes in uterine mobility and the changes during

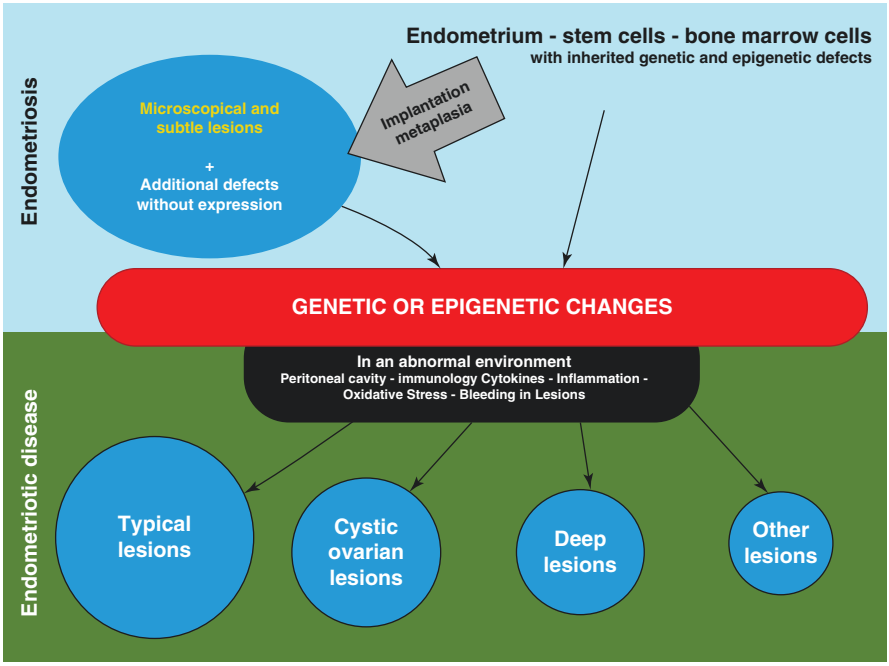

Fig. 6.2 The genetic-epigenetic theory. The original cell can be an endometrial cell or a stem cell or a bone marrow cell with their inherited genetic and epigenetic defects. These defects, together with additional acquired defects without expression, constitute the predisposition. Following implantation or metaplasia, defined as stable and transmittable changes, subtle and microscopic lesions occur. Additional genetic or epigenetic changes are required for these cells to change behavior and to progress into typical, cystic, deep, or other lesions. (Reproduced with permission from [1])

pregnancy since these effects are not corrected after surgery for deep endometriosis [158]. That the decreased NK activity in plasma remains low after surgical excision of deep endometriosis suggests that the NK cell defect is not a consequence of endometriosis [159].

During life, additional G-E incidents occur, either as occasional incidents during cell cleavage or as a consequence of environmental toxins as dioxin or radiation with known genomic and epigenetic [160] effects. Most incidents will be repaired, or the cell will become apoptotic. If the cell survives, they can accumulate a series of incidents over time. Most incidents will remain invisible since most of the molecular biological pathways are redundant [161]. Only when cumulative G-E incidents exceed a certain threshold and/or when the external stressors require more metabolic activity than permitted by the cumulative incidents abnormalities become visible, and these cells can start their development into endometriosis. This explains the clonal aspect of endometriosis lesions. This also explains the large variability within endometriosis lesions with little or high aromatase activity and with progesterone resistance varying from very severe to nonexistent.

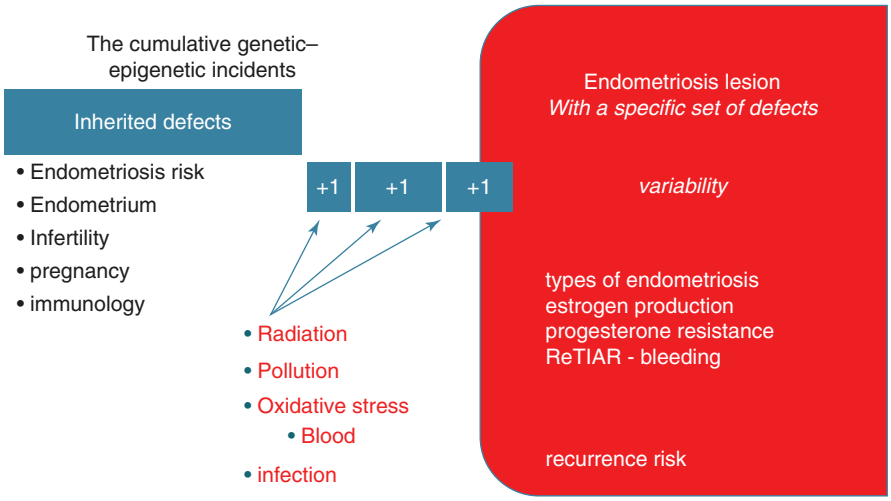

Fig. 6.3 The cumulative genetic-epigenetic incidents. Some endometriosis-associated observations can be explained by inherited defects. During life, additional defects occur because of radiation, pollution, or oxidative stress. After transcending a threshold, caused by the cumulative defects and/or an increased cellular stress and/or the abnormal environment, these cells start their growth to form endometriotic lesions which are variable macroscopically, biochemically, and clinically

The original cell is less important and can be endometrium after neonatal or adult retrograde menstruation, peritoneal or endometrial stem cells, peritoneal cells after mesenchymal-mesothelial transformation, or even bone marrow cells. What is important is that these cells are genetical-epigenetically "normal" cells which can form transient subtle lesions after implantation.

Molecular biology already has identified many potential G-E alterations which might be involved in the development of endometriosis. A comprehensive understanding of changes, however, remains hampered by the redundancy and complexity of pathways.

Our Actual Understanding of the Development of Endometriosis Lesions

The endometrium is one of the fastest growing tissue in the human body with a special relationship with the junctional zone as evidenced during placentation. Any acquired abnormality of the functionalis of the endometrium will be eliminated during menstruation. This mechanism is considered to explain the increased incidence of endometrial cancer immediately after menopause. Outside the uterus, however, such as in the peritoneal cavity these cells are no longer eliminated.

An endometrial cell or any other cell in the peritoneal cavity develops in the specific environment of the peritoneal cavity with different concentrations of

proteins and steroid hormones, with a different immunology and microbiome and an increased oxidative stress. The latter is increased by the amount of retrograde menstruation [162]. Both the microbiome, from ascending infection and from transmural migration from the intestine [82, 84, 163], and the oxidative stress have the potential to cause G-E incidents, which explains that endometriosis develops mainly in the pelvis and the relationship with a more abundant retrograde menstruation [164] causing more oxidative stress and more retraction of peritoneal mesothelial cells, thus facilitating the implantation of endometrial cells [165, 166].

The further growth of the endometriosis lesions will vary with the specific set of incidents in the lesion, such as aromatase activity and progesterone resistance, and with the environment. What is important is that also the environment such as the low-grade inflammation in the peritoneal cavity, the angiogenic factors, and the activated macrophages with their secretion products will vary with the set of incidents transmitted at birth and acquired during life. In addition, the monthly bleeding in the lesion during menstruation constitutes a specific oxidative stress which risks to cause additional G-E incidents. It, moreover, is a repetitive tissue injury that needs to be repaired [167].

Growth of typical and deep endometriosis lesions seem to be self-limiting. After a period of growth, most lesions seem to stop growing which is the case for most lesions at diagnosis. Some rare deep and cystic lesions; however, they seem very active during surgery and seem to continue growth.

The role of the intraovarian concentrations of steroid hormones in the development of cystic ovarian endometriosis must play a role, but this has not yet been adequately investigated.

The G-E theory is compatible with all observations on endometriosis today. That many of the molecular biological alterations described in endometriosis lesions are increasingly viewed as the result of genetic and epigenetic incidents lends further support to the G-E hypothesis. However, it should be stressed that the implantation and growth of endometriosis lesions and the associated inflammatory reaction could also explain some of the associated observations, such as the increased nerve density [168, 169]. Another example is the high glycodelin concentrations in peritoneal fluid which may protect early lesions from NK cell attack [170, 171] and thus could facilitate survival.

Clinical Implications of the G-E Pathophysiology

The Relationship with Ovarian Cancer

The G-E theory is a similar mechanism as those leading to cancer. Although not conclusively proven, the repetitively suggested association of cystic ovarian endometriosis with ovarian cancer is not that surprising, since endometriosis already has a series of incidents such as cancer driver mutations [123]. In addition, the emerging

association of endometriosis with pelvic infection and the demonstrated decrease in ovarian cancer after tubal ligation might suggest similar mechanisms.

Prevention of Endometriosis Onset, Recurrences, and Growth

The G-E theory suggests that a reduction of oxidative stress in the peritoneal cavity might become a prevention of endometriosis onset and recurrences. This could be achieved by oral contraception given continuously. Not yet explored are therapies as progesterone antagonists in lower doses. Also, the once popular tubal ligation, which can be performed as a 5-minute procedure under local anesthesia, might be considered when conception is no longer considered.

A reduction of the overall oxidative stress by fruit, vegetables, and other antioxidants might be considered. Understanding the relationship between food intake and the intestinal microbiome and of transmural migration of pathogens from the bowel as Shigella opens new concepts of endometriosis and food intake.

These concepts of prevention of growth and recurrences are especially important for younger women.

Treatment of Endometriosis Lesions

Typical, cystic, and deep endometriosis are three different diseases harboring a different set of G-E incidents. In addition, this set differs in each clonal lesion, which explains the marked heterogeneity in endometriosis lesions. Most deep endometriosis lesions are painful, and some not. Some typical lesions cause pain, and some not. Some deep endometriosis lesions are progressive, and most not.

Surgery is the treatment of choice if endometriosis is considered a benign tumor. However, radicality of surgery is less clear. It is conceivable that the fibrotic rim around a deep endometriosis lesion and the growing cell columns are reactive and metaplastic changes induced by the central core of tumor. This is compatible with the observation that recurrence rates of deep endometriosis are not remarkably different following conservative excision leaving a rim of fibrosis, aggressive conservative excision, and a small or a large bowel resection. If confirmed, this would be a major argument that radicality should be tailored.

Most important for medical therapy is the individualization of therapy because of the heterogeneity of endometriosis lesions. It should be realized that an analysis with statistics describing means and standard deviations will not pick up that a therapy might stimulate instead of decrease endometriosis lesions even if stimulation occurs in 20% of patients (Fig. 6.4). For this reason, we advocate to reconsider treatment if the patient does not respond sufficiently within a few months. This heterogeneity should also be reflected in the analysis of data where individual responses should be evaluated in order to detect hidden subgroups.

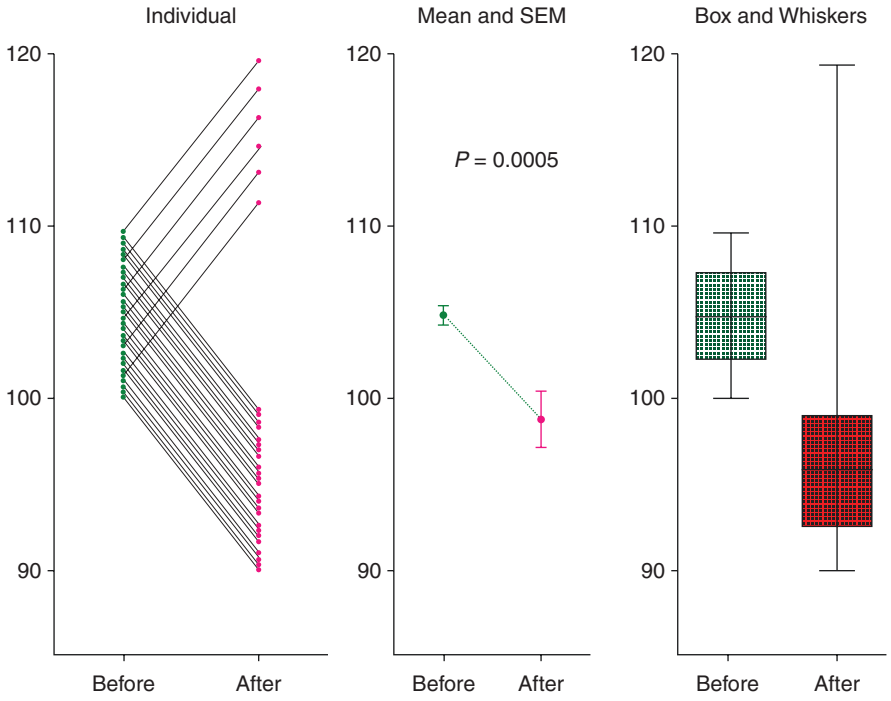

Fig. 6.4 A data set with 24 women decreasing and six increasing pain by 10% after treatment. Heterogeneity of response is obvious when the individual data are plotted but hidden when only means and SEM are given. The variability in response is suggested by box and whiskers plots. Students' t-test results in $P = 0.0005$. (Reproduced with permission from FVVO)

Discussion and Conclusions

Activation and repression of DNA transcription and the subsequent translation are complex processes with complex regulatory mechanisms. Epigenetics are stable transmissible changes in DNA expression without DNA changes [172]. This, however, permits different definitions [173]. The NIH Epigenomics Mapping Consortium [174] uses epigenetics to indicate changes in gene expression; others use it to refer to transgenerational effects and inherited expression [175]. Epigenetics is used for both reversible and for stable changes that are transmitted after cleavage. When transmitted at birth, they are called the epigenetic trait [176].

The meaning of many words used in endometriosis did change over time when new clinical and molecular-biological observations were added to the initial clinical, macroscopic, and microscopic descriptions. Metaplasia was introduced as a descriptive histological observation, without the concepts of stable, reversible, and transmissible changes. We know from stem cell research that changes during cellular differentiation can be stable and transmitted, although reversible. It is unclear whether "metaplastic" changes preceding the development of cancer are reversible

or whether they signal some stable changes which increase the risk that another incident will start the development of a malignant tumor. Metaplasia, thus, is used to indicate the (reversible) expression of environmental stress [177] and also to indicate the expression of stable genetic or epigenetic damage. If metaplasia is defined as metaplastic changes without permanent and transmissible genetic or epigenetic changes, the resulting endometriosis cells are genetically and epigenetically similar to endometrium. If, on the contrary, metaplasia indicates stable and transmissible genetic or epigenetic changes, this comes close to the G-E theory.

The G-E theory is also important for our views on nonhuman models of induced endometriosis, in both primates and rodents. These models remain valid to study the effect of abnormal environments on (normal) endometrium. Transplantation of human endometriosis into SCID/nude mice could be a model to study the development of (abnormal) endometriotic tissue in a normal or controlled environment.

In conclusion, the G-E theory of endometriosis explains endometriosis as the consequence of a cumulative set of genetic and epigenetic incidents in endometrial, stem, or other cells developing in an abnormal environment with already a specific set of G-E incidents acquired at birth. Prevention of endometriosis, thus, should focus on the prevention of new incidents through reduction of oxidative stress by retrograde menstruation and by understanding the peritoneal microbiome and the relationship with food intake and a reduction in environmental pollutants. Medical therapy should take into account the heterogeneity of lesions, and the radicality of surgery might be reconsidered.

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Conflicts of Interest None of the authors have a conflict of interest to declare.

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