2008

ÜREME TIBBI ve CERRAHİSİ DERNEĞİ

Endometriozis Patogenezi

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V. ÜREME TIBBI VE CERRAHİSİ DERNEĞİ KONGRESİ
28 - 31 Ekim 2015
Cornelia Diamond Resort
Belek, Antalya

ENDOMETRİOSİS - TANIM

- *Uterin kavite dışında fonksiyonel endometrial dokunun (bez ve stromanın) varlığı*

- Sık görülen
- Benign
- **Östrojen-bağımlı**
- **Progesterona dirençli**
- **Kronik, inflamatuar** hastalık

Eskenazi 1998
Mismer 2003
Kennedy 2005

EPİDEMİYOLOJİ

- Genel popülasyondaki prevalansı ?

- **Reprodüktif çağdaki kadınlarda "tahmini" prevalans % 3–10**
  - Tüm dünyada > 100 milyon kadın

- **Pelvik ağrısı** olan kadınlarda **% 50-70**
- **İnfertilitesi** olan kadınlarda **% 30-50**

Bulun 2009
Giudice 2004
Sangi-Haghpeykar 1995
Mismer 2004

RİSK

- **RİSKİ ARTTIRANLAR**
  - **Aile öyküsü**
  - **Nulliparite**
  - **Erken menarş (<10 yaş) / geç menopoz**
  - **Kısa menstrüel sikluslar**
  - **Uzamış mensler**
  - **Müllerian anomaliler**
  - **Uzun boy, ince vücut yapısı, düşük VKİ**
  - **Asya ve beyaz ırklar**
  - **Alkol, Kafein**
  - **PCB, Dioksin vb endokrin bozucu kimyasallar**
  - **İn utero DES maruziyeti**

- **RİSKİ AZALTANLAR**
  - Multiparite (>3)
  - Uzamış laktasyon dönemleri (>23 ay)
  - Geç menarş (>14 yaş)
  - Hispanikler ve siyahi ırk
  - Egzersiz
  - Sigara?

Mismer 2004
Treloar 2010

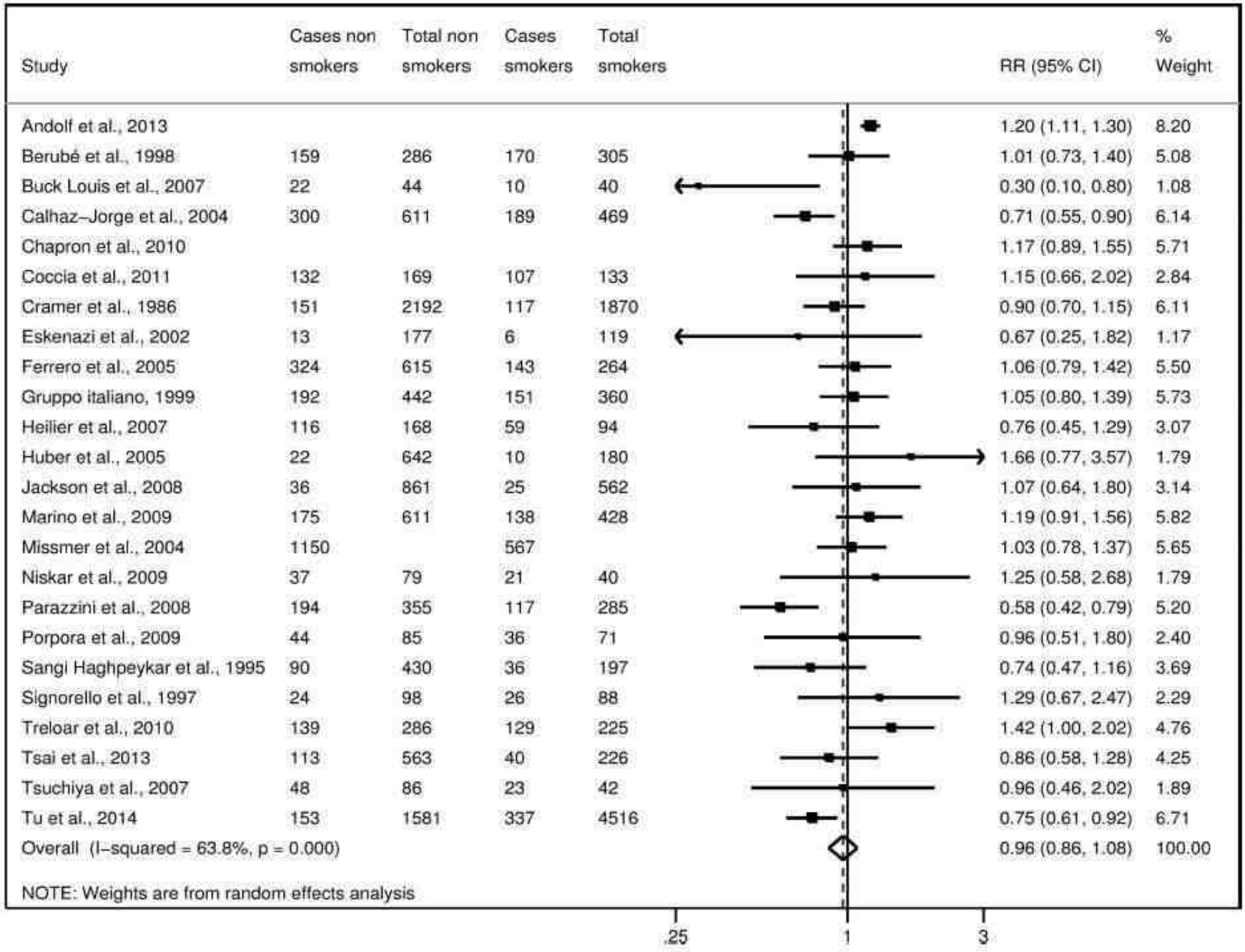
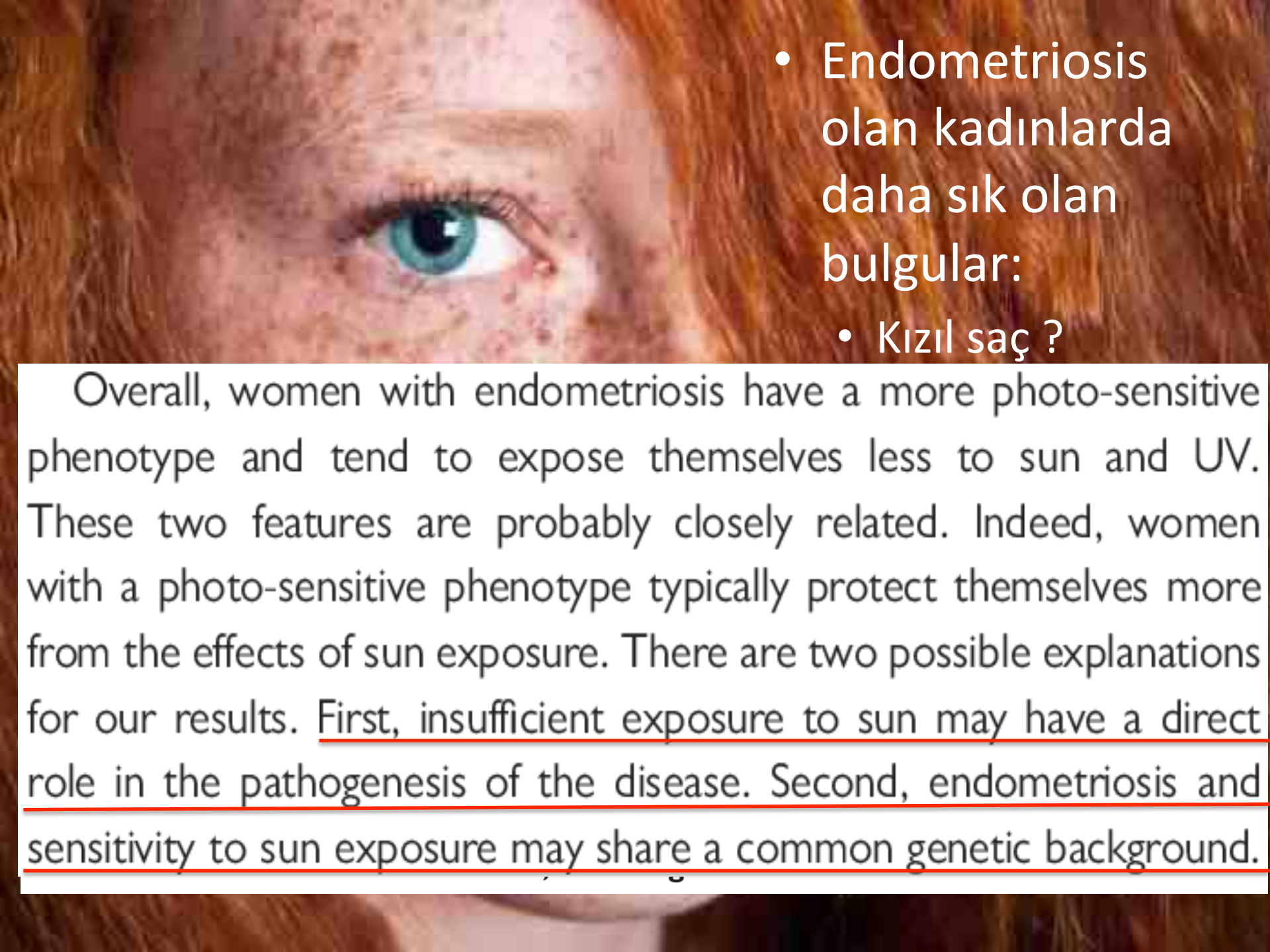


Figure 2 Study-specific and summary relative risks (RR) of endometriosis for ever smokers versus never-smokers.



- Endometriosis olan kadınlarda daha sık olan bulgular:
  - Kızıl saç ?

Overall, women with endometriosis have a more photo-sensitive phenotype and tend to expose themselves less to sun and UV. These two features are probably closely related. Indeed, women with a photo-sensitive phenotype typically protect themselves more from the effects of sun exposure. There are two possible explanations for our results. First, insufficient exposure to sun may have a direct role in the pathogenesis of the disease. Second, endometriosis and sensitivity to sun exposure may share a common genetic background.

PATOGENEZ

- Tam olarak bilinmemekte

- Tüm endometriosis olgularını açıklayan tek mekanizma yok

PATOGENEZ

- Üç klinik tip:
  - **Peritoneal Endometriosis**
  - **Endometrioma**
  - **Rektovajinal endometriotik nodül (DİE)**

- Aynı patolojik sürecin variantları?
- Farklı mekanizmalar?

TEORİLER

- Retrograd menstruasyon/implantasyon
- Kölomik metaplazi ve indüksiyon
- Vasküler disseminasyon
- İmmün disfonksiyon
- Genetik faktörler
- Çevresel faktörler

Retrograd menstruasyon/ implantasyon

- Menstrüasyonda dökülen endometrial dokunun fallop tüplerinden periton boşluğu ve pelvik yapılara ulaşması **(retrograd menstrüasyon) ve implantasyon**

Sampson, 1927

- Cerrahi skarlarda (epizyotomi, laparotomi) gelişen endometriozis (**İatrojenik transplantasyon**)

- Endometriosis sadece menstrüasyon olan türlerde (insan ve diğer primatlarda)

  D'Hooghe 2002

- Obstrüktif müllerian anomali varlığında endometriosis insidansı daha yüksek

  Olive 1987

- Fakat tüm kadınlarda retrograd mens +
  - ? % 10'unda endometriozis gelişir

- Endometriosis gelişimi için ilave faktörler gerekli
  - **Moleküler defektler** ve/veya **immün disfonksiyon**

Kölomik metaplazi ve indüksiyon

- **Meyer**, 1903
- Kölomik (peritoneal) kavite epitelinde multipotent hücrelerin endometriuma benzer hücrelere farklılanması
  - Spontan
  - Menstrüel akım veya başka uyaranla (indüksiyon teorisi)

- Premenarştaki endometriozis
- Plevral-pulmoner, ekstremitelerde, üriner ve GİS, inguinal kanal, umblikusta
- Yüksek doz östrojen alan erkekler

Vasküler disseminasyon
(hystero-adenosis metastatica)

- **Endometrial hücre/dokuların** veya
- Dolaşımdaki **kök hücrelerin**

lenfatikler veya kan damarları yoluyla dağılması

  – Nadir ekstrapelvik lezyonların açıklanmasında (akciğer, beyin)

Halban 1924

Javert 1949

Sasson 2008

İmmün disfonksiyon

- Endometrial dokular immün/inflamatuar yanıtlarla elimine edilmekten kaçarlar → Artmış ektopik hücre sağkalımı
  - **Yetersiz hücresel immünite** anormal lokasyonlardaki endometrial dokunun farkedilmemesi
  - **NK hücre aktivitesi azalarak** otolog endometrium üzerinde daha az sitotoksik etki
- Periton boşluğu ve ektopik yerleşimli endometriumda daha fazla;
  - **İnflamatuar hücre konsantrasyonu**
  - **Sitokin** (ör. IL-1, 6 ve 8; TNFler, RANTES) ve **büyüme faktörleri salınımı**
  - **İmplantların proliferasyonu**
  - **Yeni kapiller oluşumu** (ör. VEGF)

Dmowski 1994
Van Langerdockt 2002
Bulun 2009

Normal vs Endometriotik Endometrium

- Endometriozisli kadınlarda **ektopik endometriumda** ve **ötopik endometriumda** (daha hafif) fonksiyonel anormallikler (SF-1 ve ER-β promoter hipometilasyonuna bağlı)

Artmış lokal östrojen üretimi

COX-2 upregülasyonu, **yüksek lokal prostaglandin ve sitokin**

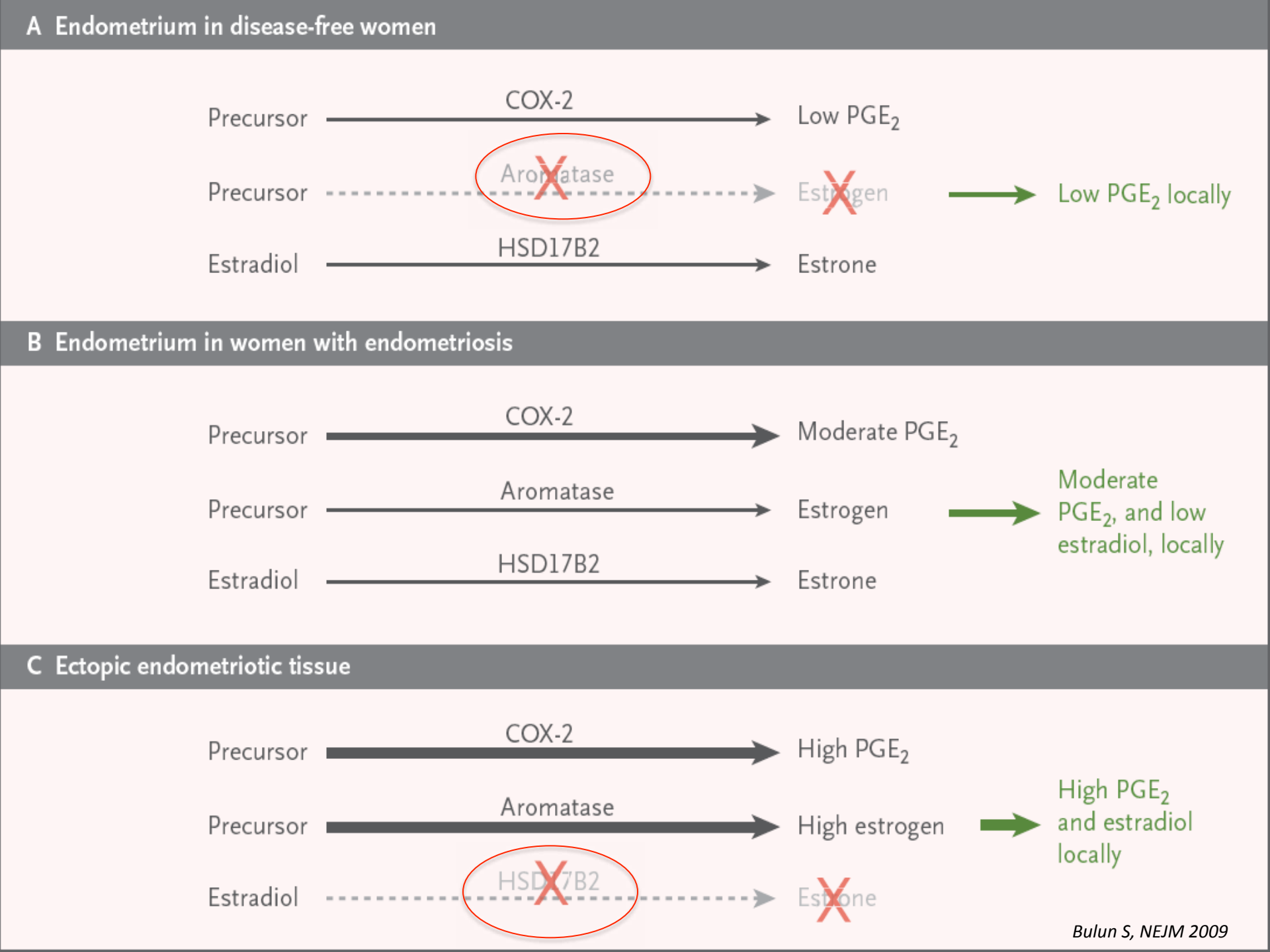
Azalmış progesteron reseptörleri ve **progesteron etkisine direnç**

Artmış alfa ve beta östrojen reseptörleri

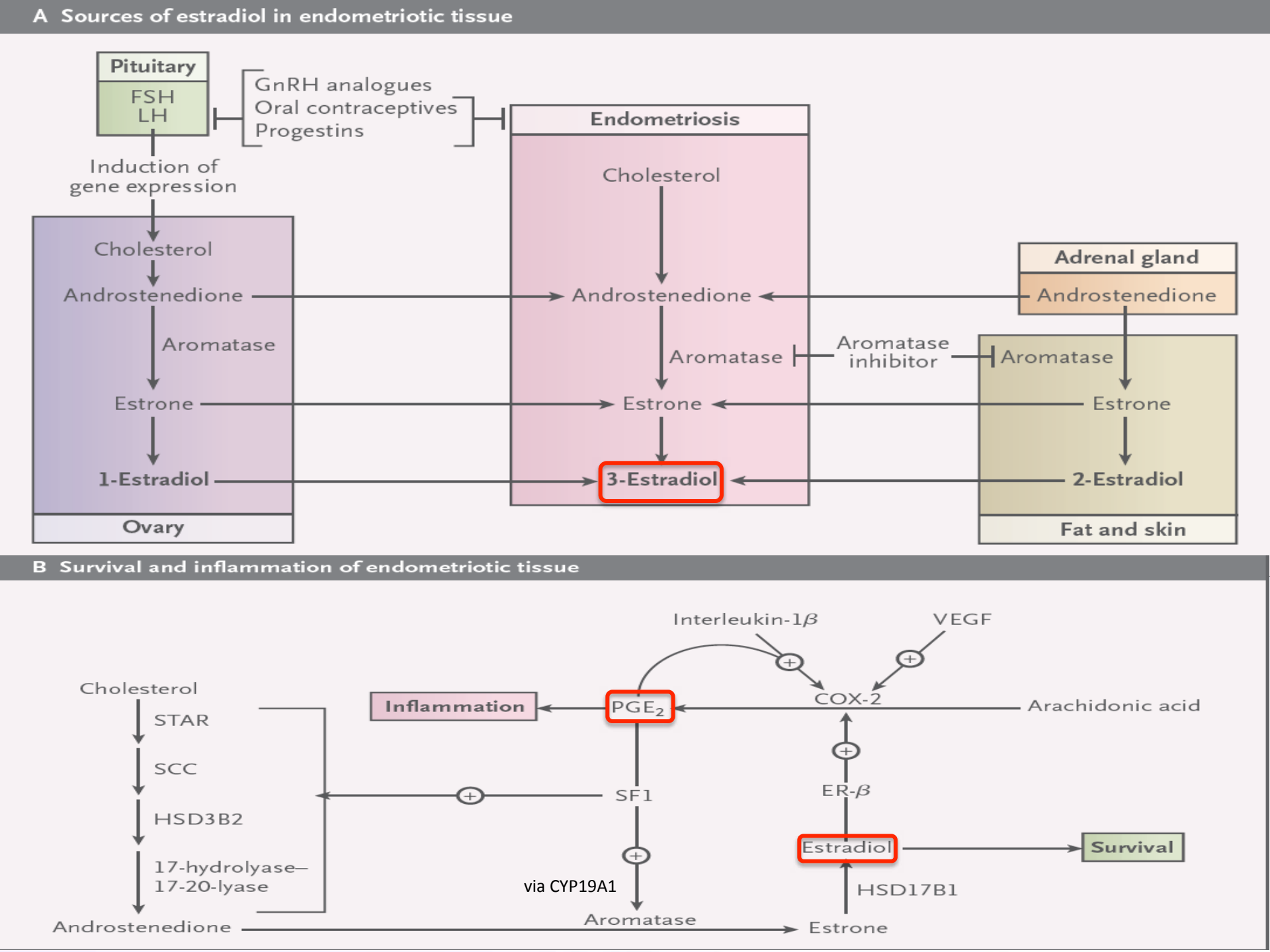
Apoptoza direnç

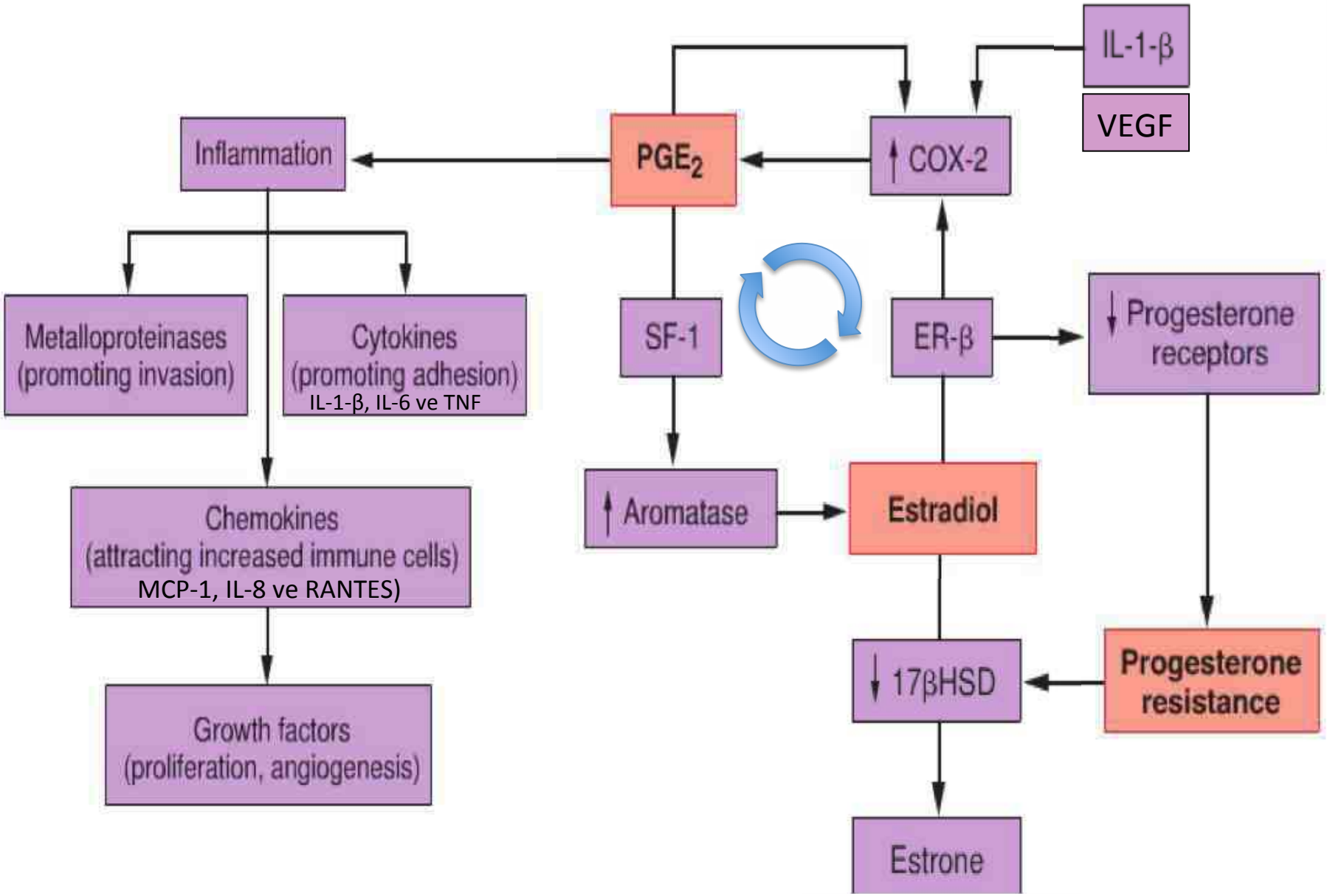
İnflamasyon

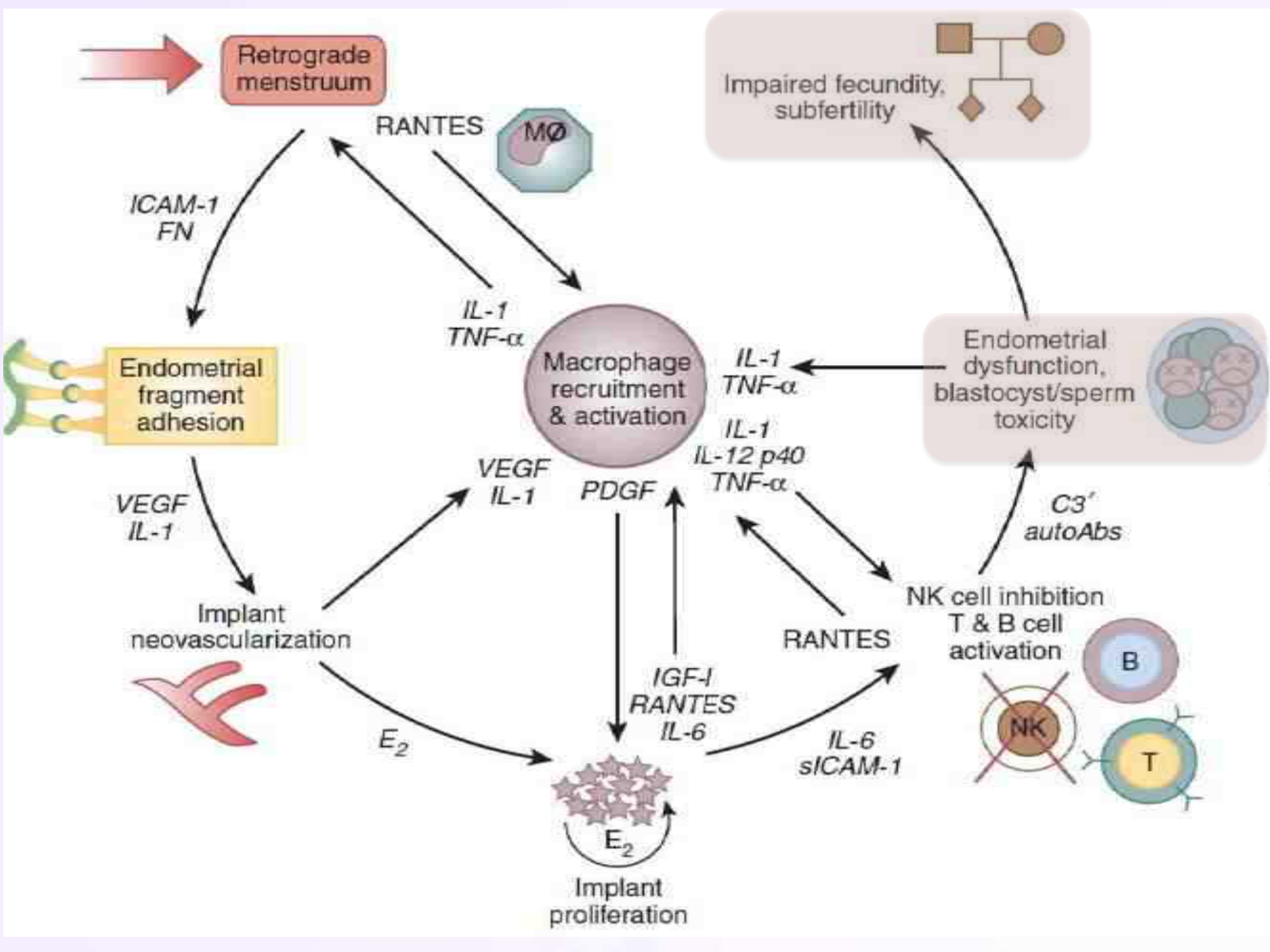
Yetersiz diferansiasyon

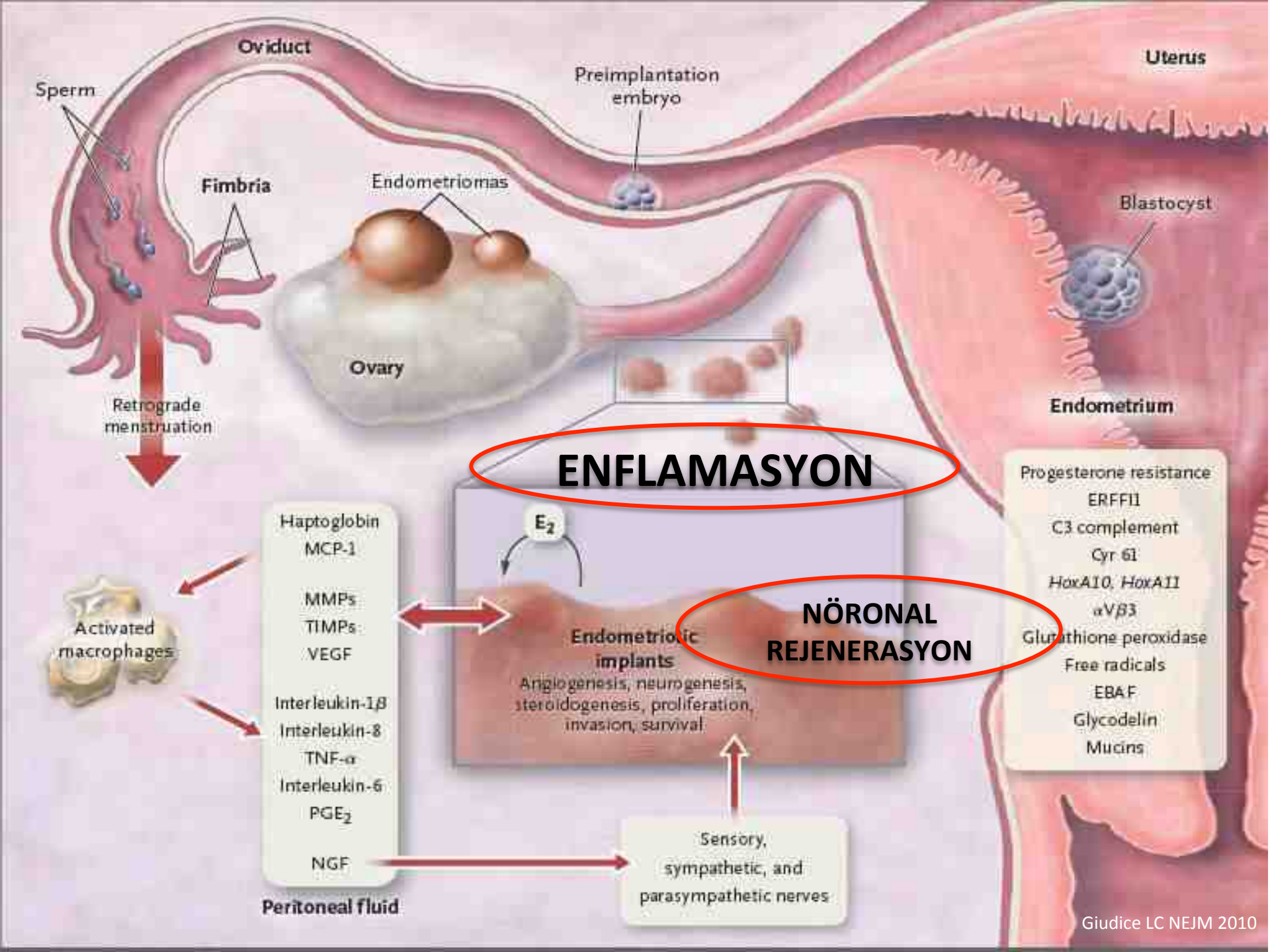


Bulun S, NEJM 2009


A Sources of estradiol in endometriotic tissue
Pituitary
FSH
LH
GnRH analogues
Oral contraceptives
Progestins
Induction of gene expression
Endometriosis
Cholesterol
Androstenedione
Aromatase
Estrone
3-Estradiol
Cholesterol
Androstenedione
Aromatase
Estrone
1-Estradiol
Ovary
Adrenal gland
Androstenedione
Aromatase inhibitor
Aromatase
Estrone
2-Estradiol
Fat and skin
B Survival and inflammation of endometriotic tissue
Interleukin-1β
VEGF
COX-2
Arachidonic acid
Inflammation
PGE2
Cholesterol
STAR
SCC
HSD3B2
17-hydrolyase–
17-20-lyase
Androstenedione
SF1
ER-β
Estradiol
Survival
HSD17B1
via CYP19A1
Aromatase
Estrone


IL-1-β
VEGF
Inflammation
PGE2
↑ COX-2
Metalloproteinases (promoting invasion)
Cytokines (promoting adhesion)
IL-1-β, IL-6 ve TNF
SF-1
ER-β
↓ Progesterone receptors
Chemokines (attracting increased immune cells)
MCP-1, IL-8 ve RANTES)
↑ Aromatase
Estradiol
↓ 17βHSD
Progesterone resistance
Growth factors (proliferation, angiogenesis)
Estrone


Retrograde menstruum
RANTES
MØ
ICAM-1
FN
IL-1
TNF-α
Macrophage recruitment & activation
Impaired fecundity, subfertility
Endometrial dysfunction, blastocyst/sperm toxicity
IL-1
TNF-α
Endometrial fragment adhesion
VEGF
IL-1
VEGF
IL-1
PDGF
IL-1
IL-12 p40
TNF-α
C3′
autoAbs
Implant neovascularization
RANTES
NK cell inhibition
T & B cell activation
B
NK
T
IGF-I
RANTES
IL-6
E2
IL-6
sICAM-1
E2
Implant proliferation



Giudice LC NEJM 2010

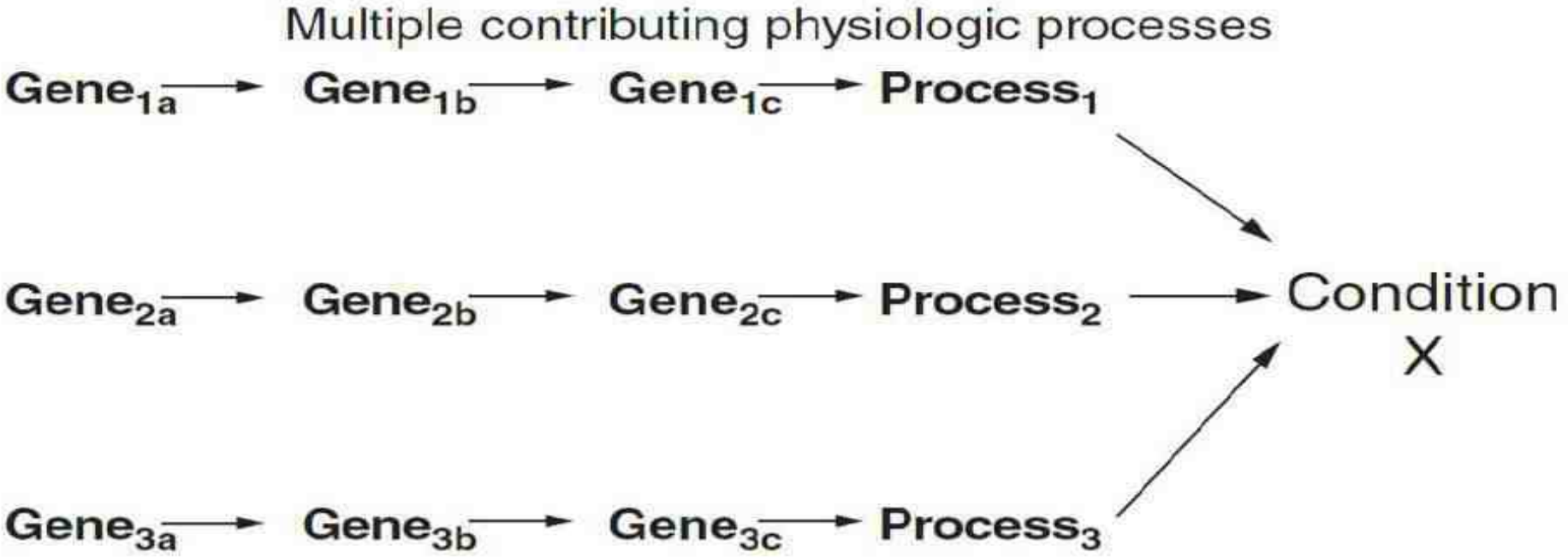
Genetik faktörler

- **Ailevi yatkınlık** bilinmektedir
- **1^0 yakınında endometriozis olanlarda genel topluma göre x 7 kat daha fazla** (%7 vs %1)
- İkizlerde konkordans

Simpson 1980
Campbell 2001
Nyholt 2012

Genetik faktörler

- Genetik faktörler muhtemelen bireyin endometriosise yatkınlığını etkilemekte
  - Multifaktöryel **poligenik kalıtım**



Genetik faktörler

- 17'nci kromozomda artmış anöploidi ve LoH (Loss of Heterogenity)
- p53 ve TOB1 (tümor süpresyon genlerinde azalma)
- C-ERBB2 artması (protoonkogen)
- Wilms' tümör 1 transkripsiyon faktörü (WT1)
- (ER)-alfa daki Pvu2 polimorfizmindeki homozigotizm endometriozislilerde az
- PROGIN ler (Progesteron Reseptör Varyantı)
- ERβ 80 kat fazla
- PR-B 48 kat az eksprese ediliyor
- HOXA10 hipometilasyonlu
- Azalmış Oksidatif stress genleri
- Azalmış WNT (Wingless-related integrated site)
- Azalmış MAP (Mitojen aktive edilmiş protein) kinaz
- Azalmış Glikodelin mRNA ekspresyonu
- Artmış EGR-1 (Early Growth Response)
- IL-1β > TOB1 supresyonu (tumor supressor gen) (normalde etkilenmez)

Simpson 1980
Campbell 2001
Nyholt 2012

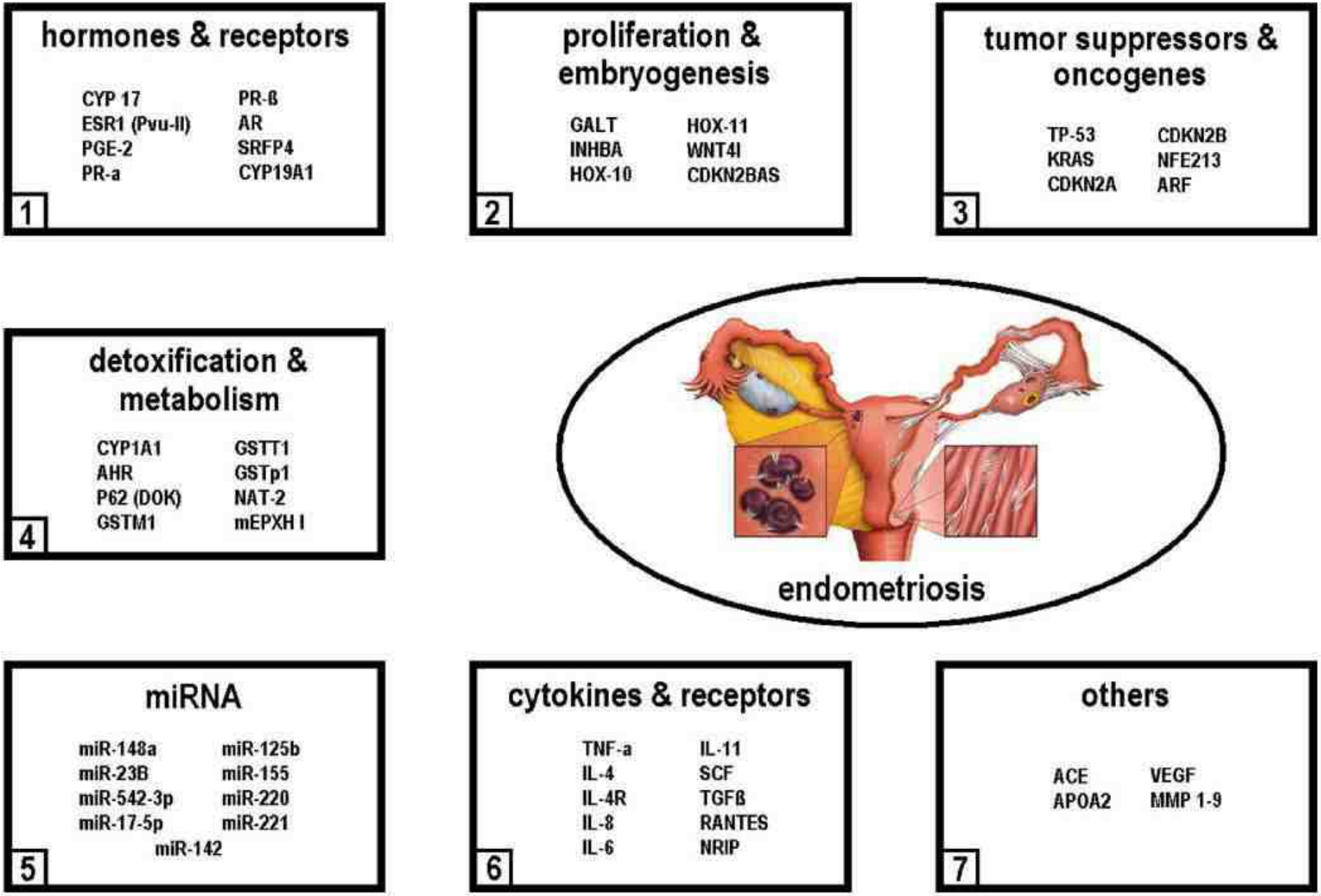
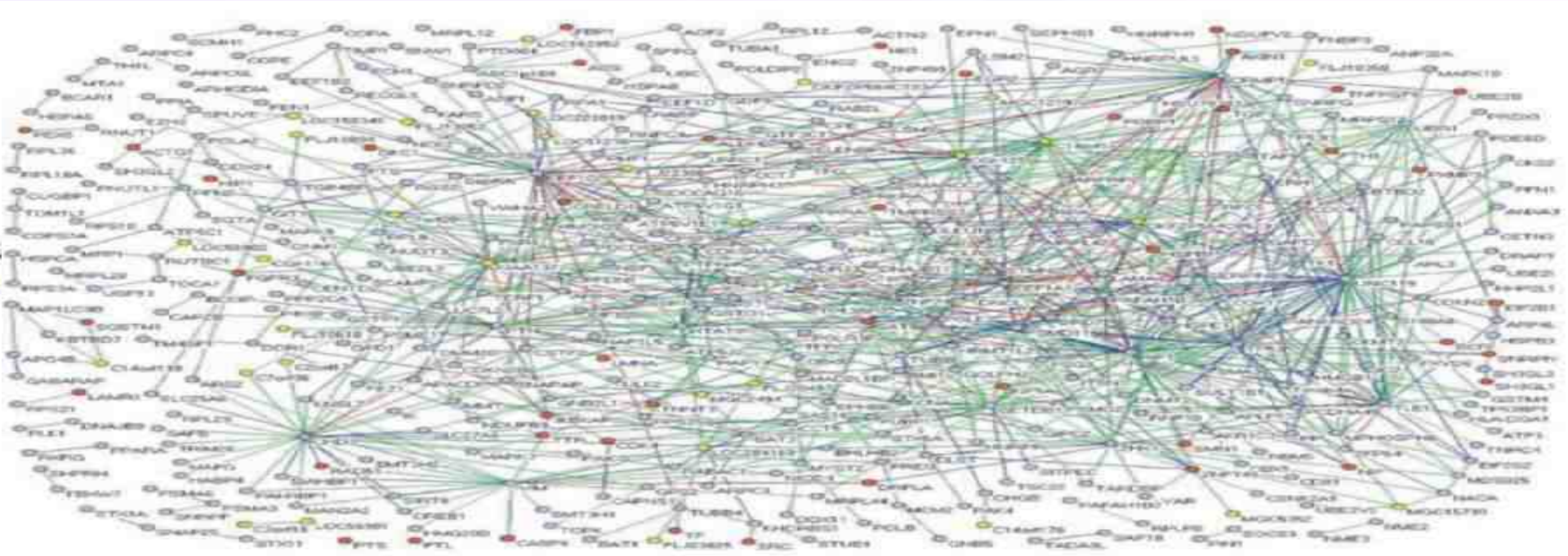


Fig. 1. The gene nets associated with pathogenesis of endometriosis [14,20,28].

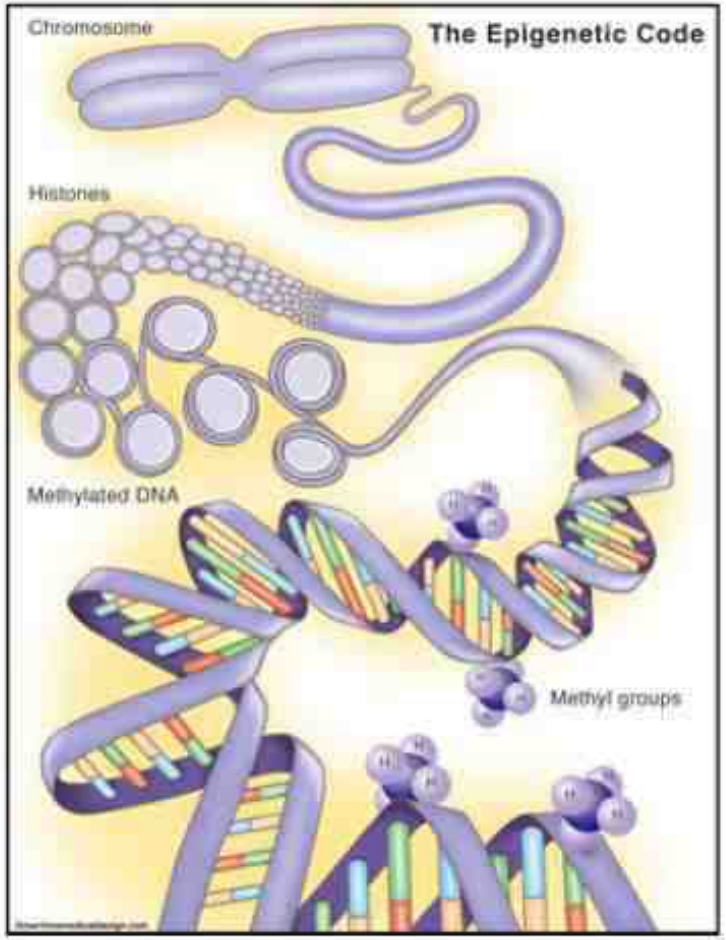
Genetik faktörler

- Çeşitli genetik polimorfizmler tanımlanmış fakat hastalık oluşumundaki rolleri ?
- Günümüzde genetik çalışmaların endometriosis tanısı ve yönetiminde klinik rolü henüz yok



Might Endometriosis be an Epigenetic Disorder?

- **Epigenetics:**
  - **Changes in methylation status of promoters of genes for transcription**
  - **Changes in histones on the chromatin**
    - Acetylation
    - phosphorylation,
    - methylation
    - Ubiquitination
    - ADP-ribosylation
- **Transgenerational**



Gene silening:
DNA methylation
histone deacetylation

Nezhat 2015

Human Reproduction, Vol.25, No.6 pp. 1528–1535, 2010
Advanced Access publication on March 23, 2010 doi:10.1093/humrep/deq044

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

A prospective study of dietary fat consumption and endometriosis risk

Stacey A. Missmer[1,2,3,*], Jorge E. Chavarro[1,4], Susan Malspeis[1,3], Elizabeth R. Bertone-Johnson[5], Mark D. Hornstein[2], Donna Spiegelman[3,6], Robert L. Barbieri[2], Walter C. Willett[1,3,4], and Susan E. Hankinson[1,3]

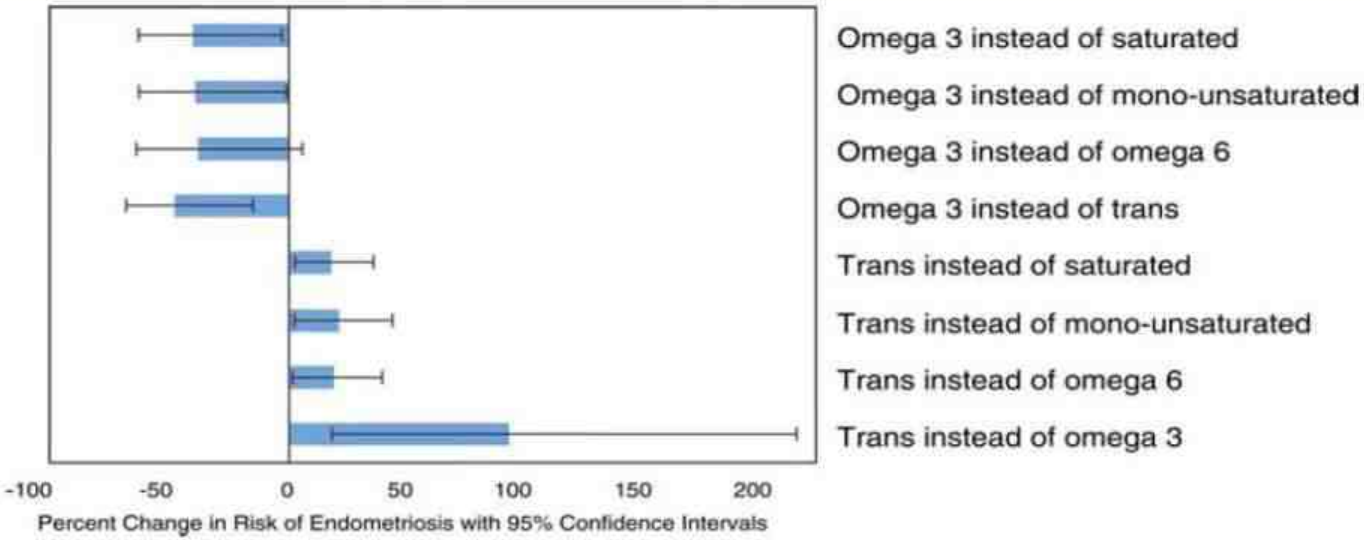
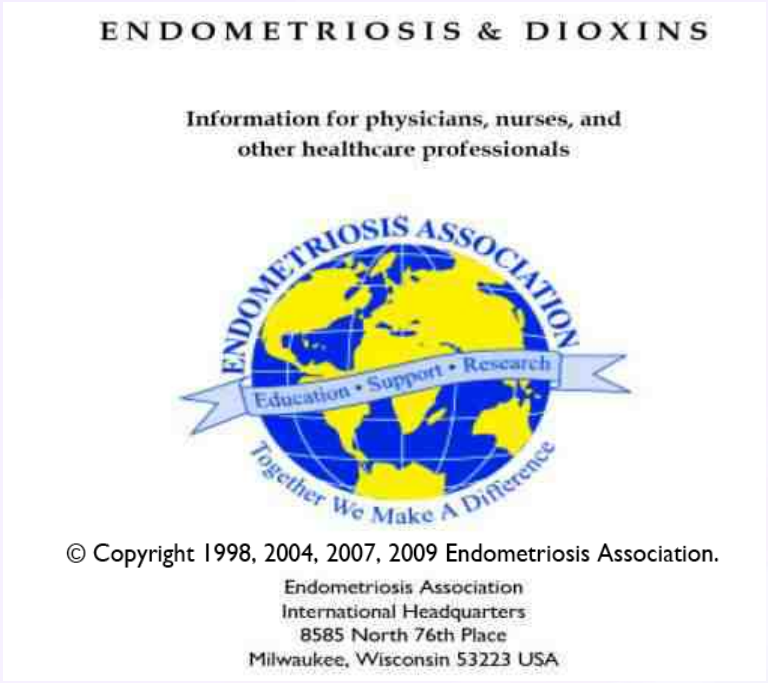


Figure 1 Impact of fatty acid substitution on the risk of endometriosis.

Estimated percent changes in the risk of laparoscopically confirmed endometriosis associated with isocaloric substitutions of 1% of energy from one dietary component for another. The I bars represent 95% CIs.



ENDOMETRIOSIS & DIOXINS

Information for physicians, nurses, and other healthcare professionals

ENDOMETRIOSIS ASSOCIATION
Education • Support • Research
Together We Make A Difference

Endometriosis Association
International Headquarters
8585 North 76th Place
Milwaukee, Wisconsin 53223 USA

ENDOMETRIOSIS & DIOXINS

Information for physicians, nurses, and other healthcare professionals

The Environmental Protection Agency (EPA) stated in its *Draft Dioxin Reassessment* (1994) that the "general population's current body burdens and exposures of dioxin are already at levels which affect our health." One of the health effects EPA specifically identified was "a higher probability of experiencing endometriosis and the reduced ability to withstand an immunological challenge."[1]

Incidence Is Rising Dramatically.

- **Hormonal olarak aktif kimyasallar (örn. dioksinler vd kimyasallar) hormon etkilerini taklit edebilir veya endokrin / immün sistemlerde disfonksiyonlara yol açabilir**
  - Endüstrileşmiş ülkelerde puberte başlangıç yaşı küçülüyor

What Are Dioxins?

According to the EPA, dioxins are the most potent synthetic carcinogens yet tested.[8] Dioxins are a class of chemicals with similar properties; these include the parent compound—2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)—and certain types of *chlorinated dibenzodioxins*, *dibenzofurans*, and *polychlorinated biphenyls (PCBs)*. Whereas PCBs are man-made (and act like dioxin in the body and *bioaccumulate*), dioxins are an accidental byproduct of a multitude of industrial processes in which chlorine is present, such as municipal and medical waste incineration, chemical and plastics manufacturing, pesticide and herbicide production, and pulp/paper bleaching.[9]

Major sources of exposure

Once created, dioxins concentrate dramatically in the food chain. Dioxins contaminate beef, fish, poultry, and dairy products. Animals consume pesticide- and herbicide-laden food, and humans consume animals and fish, our primary exposure to dioxin.[1] Dioxins are measured in fish at levels up to a million times greater than those found in the surrounding water. The remainder of human exposure occurs from contaminated air, water, and bleached paper products.

Bioaccumulation in the body

In the process of bioaccumulation, dioxin, even in very low doses, builds up in the body over time, as it concentrates in fatty tissues. Dioxin also *biomagnifies* through the food chain as higher organisms consume plants and small animals.[2] According to the EPA, the half-life of TCDD in the body (the time to rid the body of half of the amount of bioaccumulated dioxin) is about seven years, while the half-life of PCBs is variable.[2,15,16]

"[19]It is possible for a woman to "excrete half of her accumulated amount of dioxin during lactation."

In general, our body burden of dioxins increases as we get older. The time of exposure to TCDD during our lives may also affect our body burden of dioxin as adults. A recent study (Seveso, Italy) showed that girls younger than age 10, who were exposed to dioxin, retained higher levels of dioxin later as adults, as compared to women not exposed until teen or adult years.[17]

Studies have shown that humans and wildlife are exposed to a myriad of dioxin chemicals. How do we determine our total exposure to dioxins? The toxicity of individual dioxin-like chemicals is assessed using a toxic equivalency

Behavior of dioxins in the body

Dioxins interfere with the cell's gene processes. Entering a cell, dioxins bind to the aryl hydrocarbon receptor protein, or AhR, which is present in many parts of the body including liver, lungs, lymphocytes, and placenta.[21] Once bound to the AhR, dioxins can move freely inside the cell, and when binding to DNA inside the nucleus, they are able to switch genes on and off.[21,22] The genes targeted by dioxins influence hormone metabolism and growth factors, and thus affect reproduction, endocrine, and immune functions.[9,22]

Dioxin Exposure and Endometriosis

A 1992 study analyzed rhesus monkeys exposed for four years to 5 ppt and 25 ppt of TCDD, the most toxic form of dioxin. [23] Association researchers concluded that "the incidence of endometriosis was directly correlated with dioxin exposure and the severity of disease was dependent upon the dose administered."[23] This study demonstrated that "chronic exposure to the chemical toxin dioxin is directly correlated with an increased incidence in the development of endometriosis in rhesus monkeys."[23]

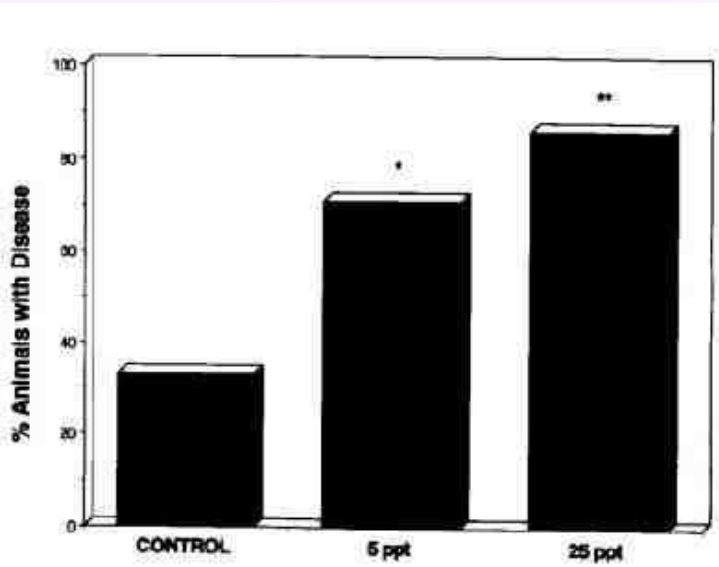


FIG. 1. Incidence of endometriosis in dioxin-exposed rhesus monkeys. Disease was evaluated at the time of diagnostic laparoscopy ($n = 17$) or from autopsy notes ($n = 3$). χ^2 analysis demonstrated significant differences between groups in absolute percentages of animals exhibiting endometriosis. *$p < 0.17$, comparing control and 5 ppt animals. **$p < 0.05$, comparing control and 25 ppt animals.

Changes in immune status of dioxin-treated animals correlated with elevated serum concentrations of dioxin (TCDD) and certain PCBs.[38] The animals with high serum levels of certain PCBs also had more endometriosis and the severity of the disease correlated with the serum level of certain PCBs.[38]

Çevresel faktörler

Executive Summary to EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals

A. C. Gore, V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller

Endocrine Reviews Received August 27, 2015. Accepted September 2, 2015.

- **Endokrin bozucu kimyasallar** çevrede, gıdalarda, su kaynaklarında mevcut
- Etkileşimle hormon biyosentezi, metabolizmasında değişiklik ve anormal etkiler

Çevresel faktörler

Endokrin bozucu kimyasallar geniş bir grup:

- **Pestisitler** (metoksiklor, klorpiriföz, **DDT**)
- **Endüstriyel çözücüler / lubrikanlar ve yan ürünleri**
  - Poliklorine bifeniller (**PCBs**)
  - Polibromine bifeniller (PBBs)
  - **Dioksinler**
- **Plastikler** [bisfenol A (**BPA**)]
- **Plastikleştiriciler** (**fitalatlar**)
- **Fungisitler** (vinklozolin)
- **İlaçlar** [diethylstilbestrol (**DES**)]

Endometriozis ile ilişkisine dair giderek artan kanıt

Çevresel faktörler

- Paradoksal masumiyet karinesi

  "***Bir kimyasal aksi ispatlanmadıkça güvenli olarak kabul edilmemelidir***"

  •Tüm kimyasallar endokrin bozucu değildir fakat yeni bir bileşiği kullanmadan önce güvenilir kanıtlar olmalı

  –Gıda saklamada

  –Su şişelemede

  –Sağlık ve güzellik ürünlerinde

  –Ev aletlerinde

- Daha önce sağlıksız olduğu için **BPA (Bisfenol A)** yerine kullanılmaya başlanan **BPS**'nin de deneysel çalışmalarda eşdeğer endokrin bozucu etkileri gösterilmiştir

Gore AC, Endocrine Reviews, 2015

REVIEW

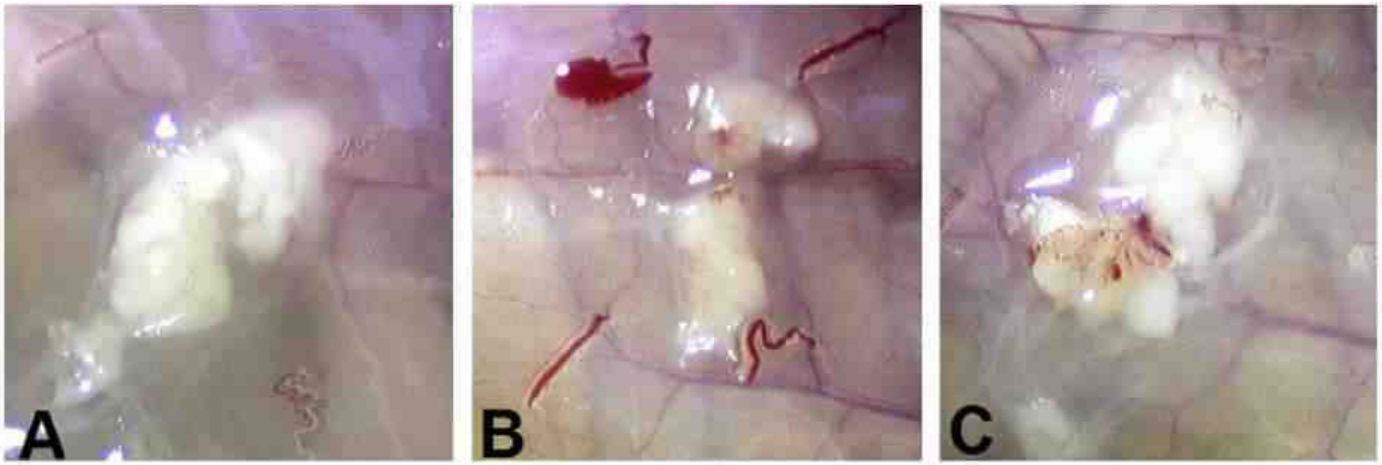
Dioxin may promote inflammation-related development of endometriosis

Kaylon L. Bruner-Tran, Ph.D., Grant R. Yeaman, Ph.D., Marta A. Crispens, M.D., Toshio M. Igarashi, M.D., Ph.D., and Kevin G. Osteen, Ph.D.

Women's Reproductive Health Research Center, Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville, Tennessee

FIGURE 3

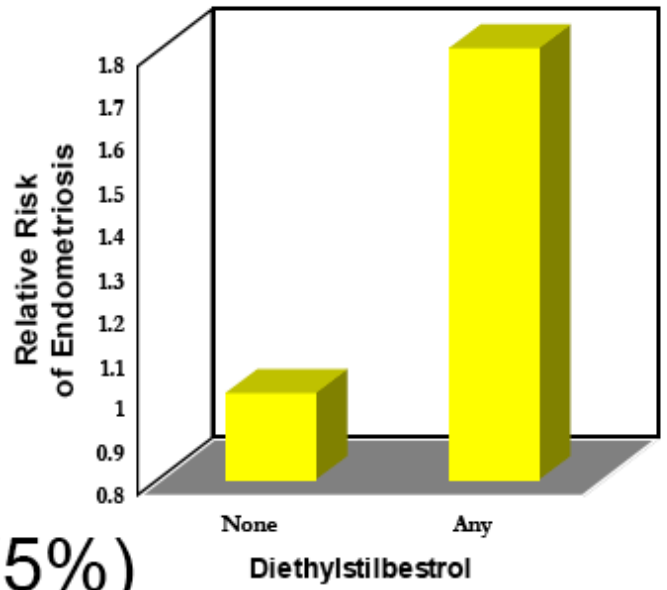
Experimental endometriosis established in nude mice: gross appearance of experimental endometriosis 24 hours after injection of (**A**) normal proliferative endometrium treated with 1 nM estradiol, (**B**) estradiol-treated tissue from a woman with endometriosis, or (**C**) endometrium from a normal woman treated with estradiol and TCDD before injection.



Bruner-Tran. Dioxin and endometriosis. Fertil Steril 2008.

In Utero Exposure to DES Increases a Woman's Risk of Endometriosis as an Adult

Nurses' Health Study II



Prospective cohort study

- 116,678 female nurses
- Baseline questionnaire in 1989
- Age range in 1989 = 25 – 42 yo
- Follow-up in 2-year intervals

Prevalence at baseline = 6,203 (5%)

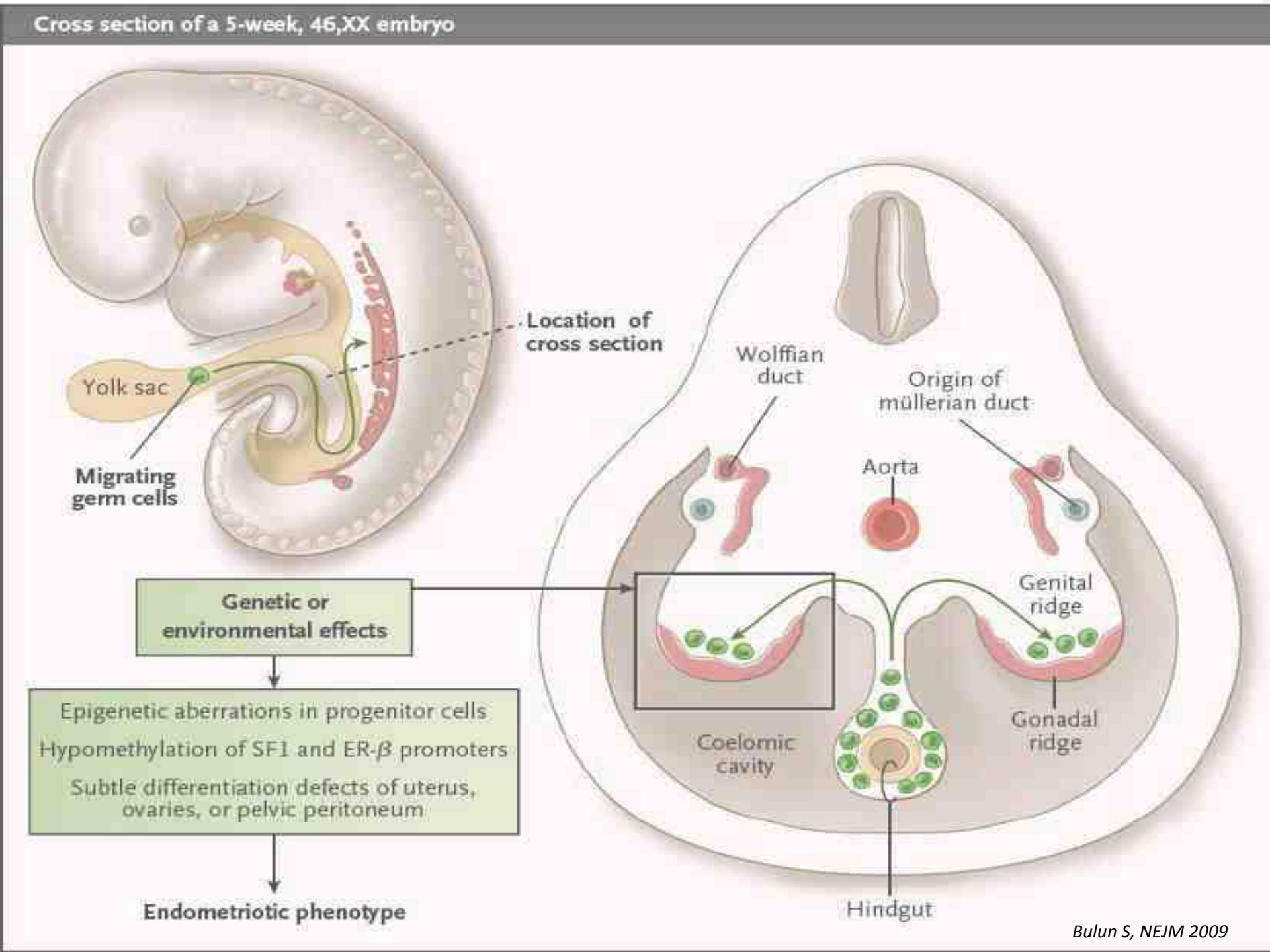
Incidence: 2,941 laparoscopically confirmed cases

Pain symptoms prompted diagnosis = 77%

Infertility work-up prompted diagnosis = 23%

- Exposure to DES: 80 % increased risk of endometriosis
- Low birth weight
- Earlier menarche

Missmer et al., Fertil Steril 2004



Bulun S, NEJM 2009

NE YAPILABİLİR?

- Plastik kod 7 az kullan
- Suyu cam şişede al-evde su filtresi
- İşlenmiş gıdayı kısıtla, kendi meyve sebzeni üret
  - Herbisit, pestisit, gübre, taze-transportsuz
- Alışverişte pl torba, duşta pvc perde, poşet çay ⃠
- Çamaşır, bulaşık, temizlik sıvıları

GELECEKTE?

- Endometriozisin önlenmesi?
- Cerrahi olmadan tanı konulabilmesi?
- Targeted tedaviler

- Endometriozis patogenezi ndeki hücresel ve moleküler mekanizmalar anlaşıldıkça

  lokal bir bozukluktan çok kompleks kronik

  sistemik bir hastalığa evrimleşecek


29 EKİM
CUMHURİYET BAYRAMINIZ KUTLU OLSUN

TEŞEKKÜRLER