ENDOMÉTRIOSE: FACTEURS GÉNÉTIQUES ET FAMILIAUX

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Théories physiopathologiques de l'endométriose

No.	Theory/hypothesis	Pathophysiology	References
1	Transplantation	Retrograde menstruation	Sampson [5]
2	Immunologic	Failure to destroy endometrium cells in peritoneal cavity	Tariverdian et al. [6]
3	Toxicologic	Pro-inflammation cytokine stimulation	Foster et al. [7]
4	Metaplasia	Dormant stem-cells in peritoneum epithelium	Meyer [9]
5	Dormant embryonic cell	Dislocation of endometrium cells outside the uterine cavity	Signorile et al. [10]
6	Denervation-reinnervation	Abnormal contractility of uteri muscles	Quinn [11]
7	Hormonal	deregulation of sex hormones balances	Dizerega et al. [12]
8	Infection	Inflammation of pelvic epithelium caused by microbial infection	Chaudhury and Chakravarty [13]
9	Genetic	Candidate genes mutations and signaling pathway impairments	Rahmioglu et al. [14]; Kim and Yim [15]
10	Epigenetic	Impairment of gene regulation	Guo [16]

V.S. Baranov et al./European Journal of Obstetrics & Gynecology and Reproductive Biology 185 (2015)

Génétique et endométriose: Agrégation familiale

AUTEURS	SOEURS	MERES
Simpson (1980)	9/153 (5,8 %) Témoins (1 %)	10/123 (8,1 %) Témoins (0,9 %)
Moen (1993)	25/523 (4,8 %) Témoins (0,6 %)	20/515 (3,9 %) Témoins (0,7 %)
Moen (1993)	75 % (monozygote)	
Oxygène Study (1997)	87 % (monozygote)	

Génétique et endométriose: Etude de liaison

- Type BRCA1-2
- Plus la distance de 2 gènes est courte moindre est le risque de « crossing over ».
- Etudes de familles atteintes d'endométriose.
- Découverte du locus majeur 10q26 et 20p13

Etude d'association génétique. Gènes impliqués dans l'endométriose

1 — hormones & receptors

CYP 17	PR-ß
ESR1 (Pvu-II)	AR
PGE-2	SRFP4
PR-a	CYP19A1

2 — proliferation & embryogenesis

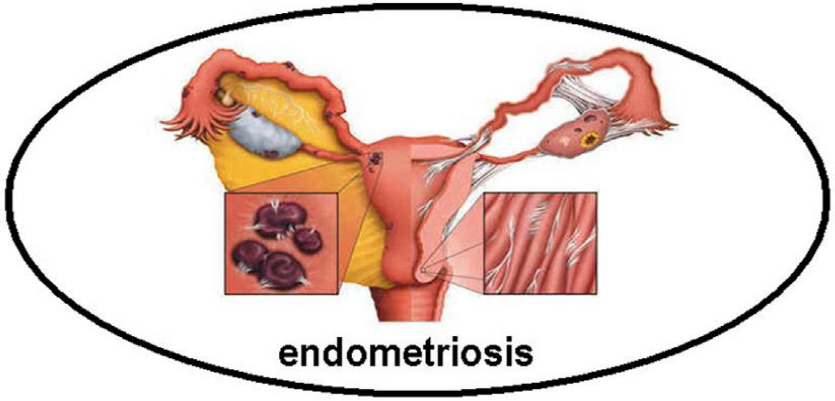
GALT	HOX-11
INHBA	WNT4I
HOX-10	CDKN2BAS

3 — tumor suppressors & oncogenes

TP-53	CDKN2B
KRAS	NFE213
CDKN2A	ARF

4 — detoxification & metabolism

CYP1A1	GSTT1
AHR	GSTp1
P62 (DOK)	NAT-2
GSTM1	mEPXH I



5 — miRNA

miR-148a	miR-125b
miR-23B	miR-155
miR-542-3p	miR-220
miR-17-5p	miR-221
miR-142	

6 — cytokines & receptors

TNF-a	IL-11
IL-4	SCF
IL-4R	TGFß
IL-8	RANTES
IL-6	NRIP

7 — others

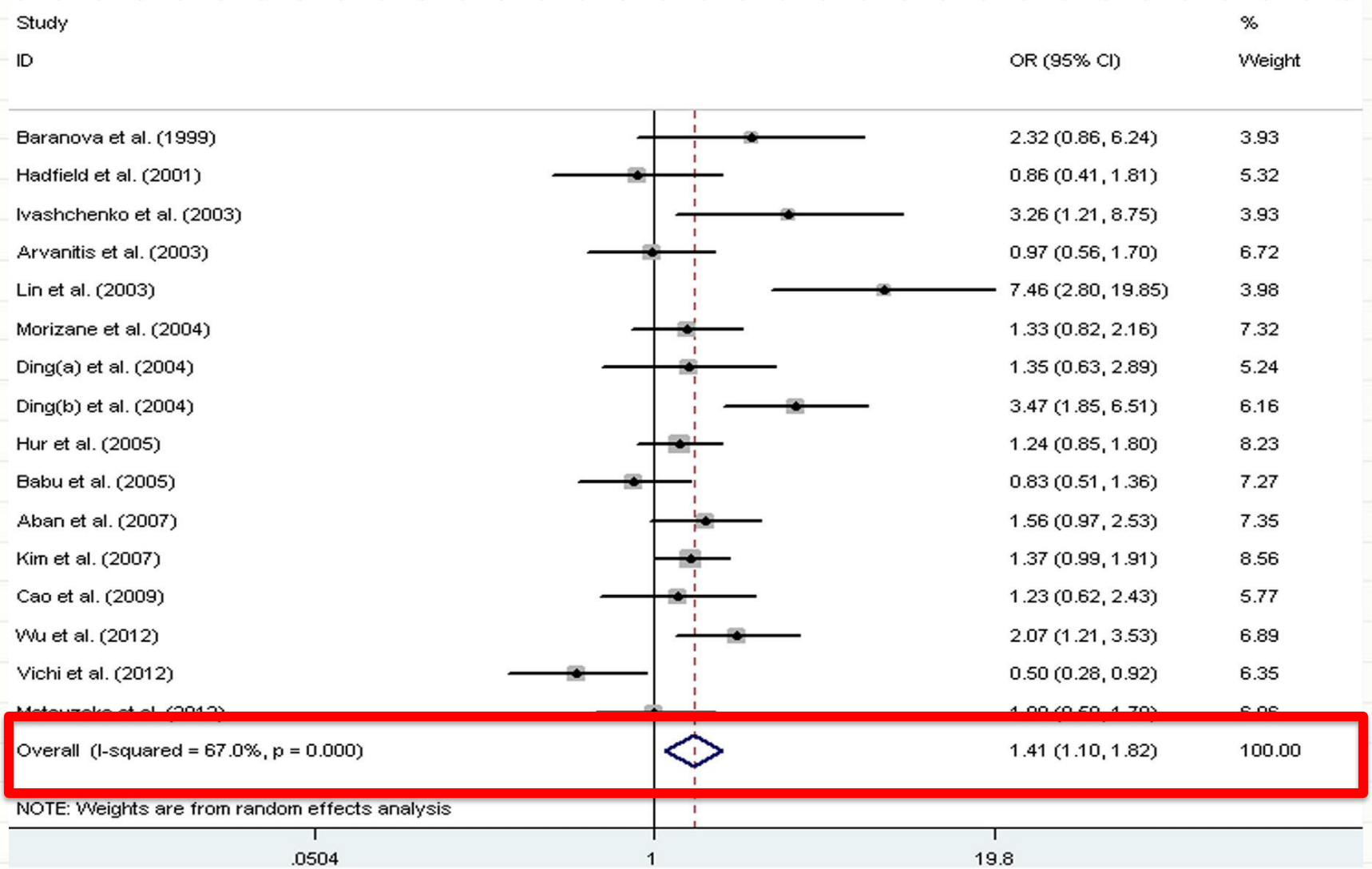
ACE	VEGF
APOA2	MMP 1-9

V.S. Baranov et al./European Journal of Obstetrics & Gynecology and Reproductive Biology 185 (2015)

Génétique et endométriose: Etude d'association génétique

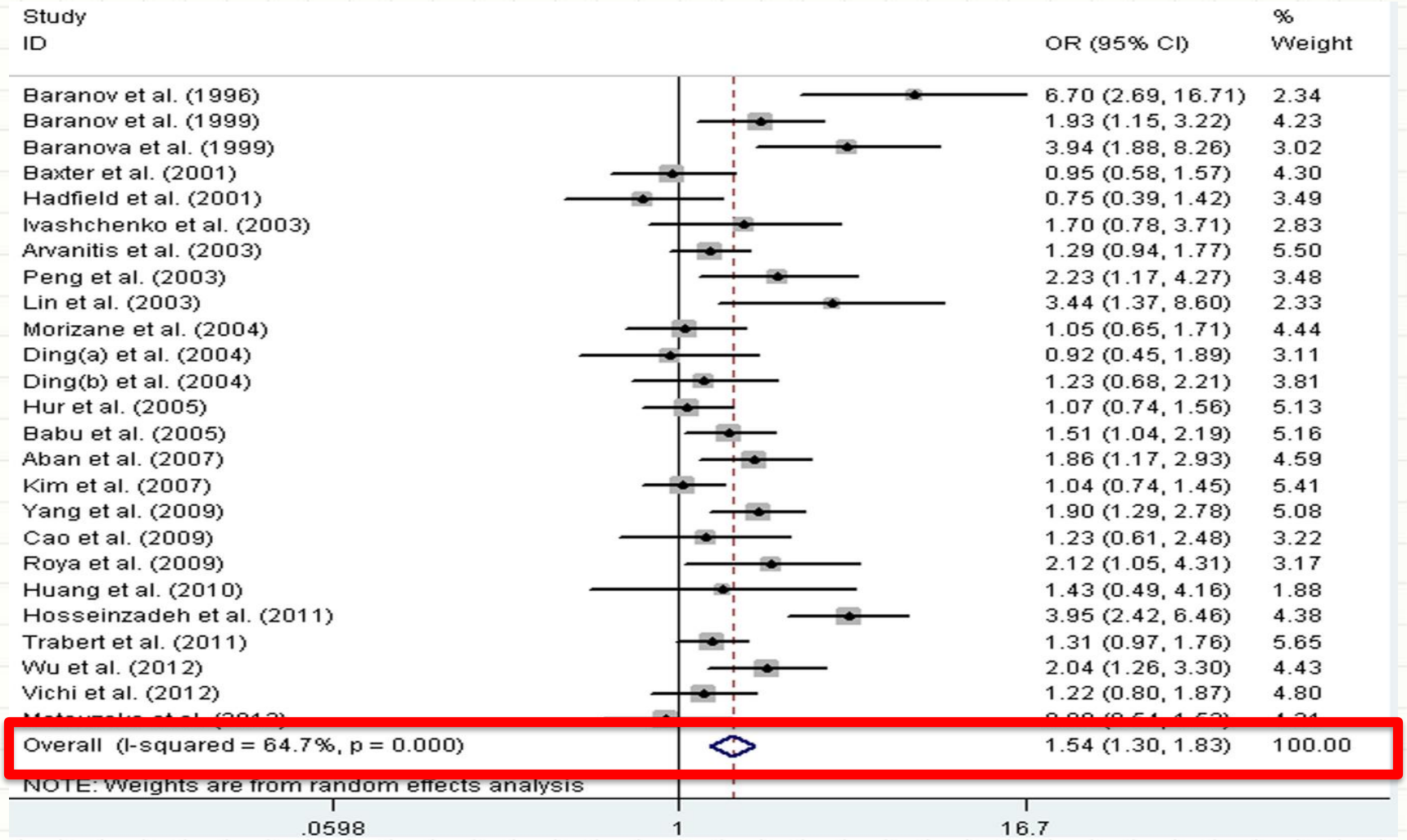
- Gènes candidats choisis sur la base de la pertinence physiopathologique.
- Etude du polymorphisme en comparant une population atteinte vs population témoins (RE, TNFα, IL6, IL 10).
- Perturbateurs endocriniens: Polymorphisme des gènes de détoxifications (GSTM1 et GSTT1).

Méta-analyse évaluant GSTT1 génotype et le risque d'endométriose



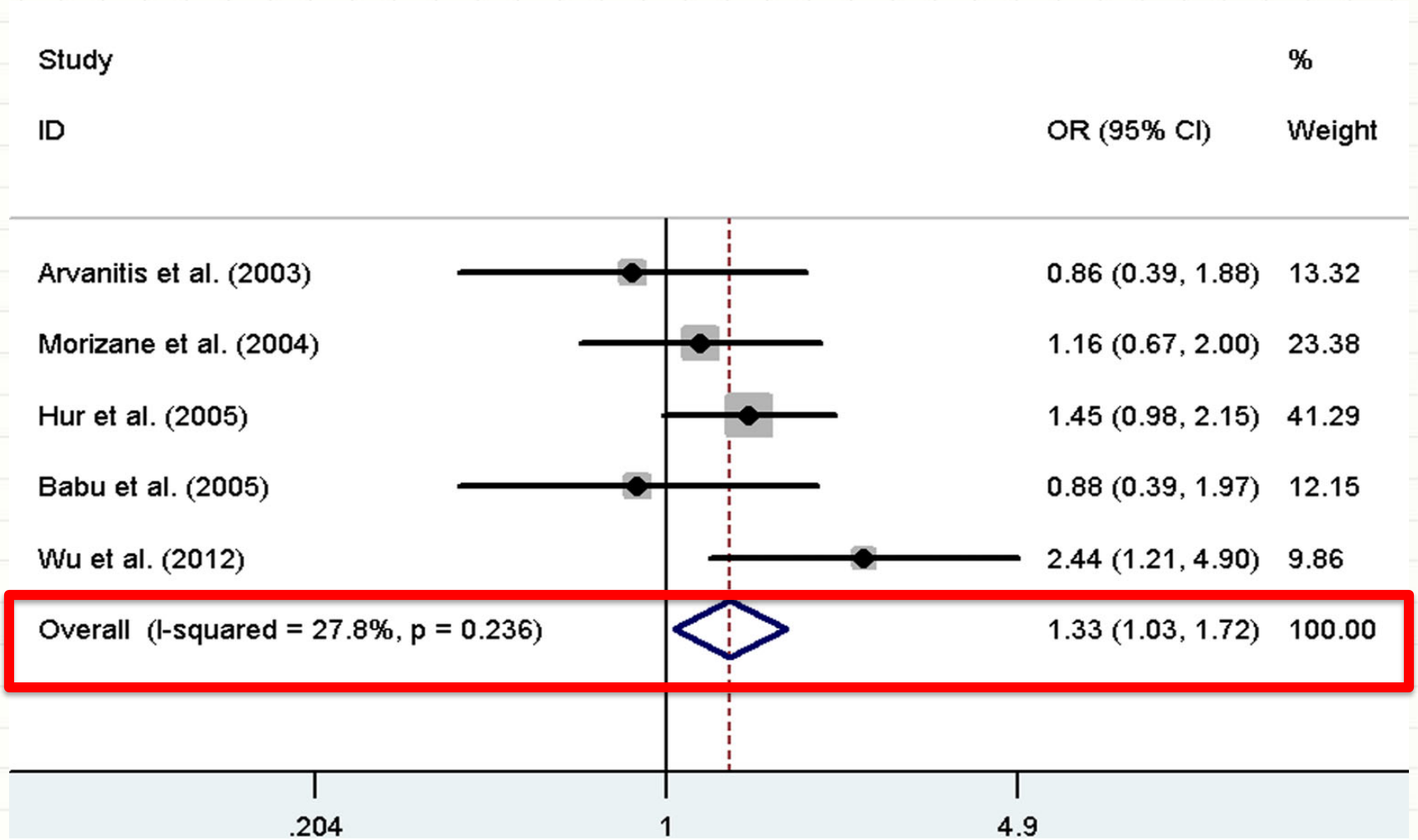
Zhu et coll, PLOS one 2014

Méta-analyse évaluant GSTM1 génotype et le risque d'endométriose



Zhu et coll, PLOS one 2014

Méta-analyse évaluant l'association GSTT1-GSTM1 génotype et le risque d'endométriose



Zhu et coll, PLOS one 2014

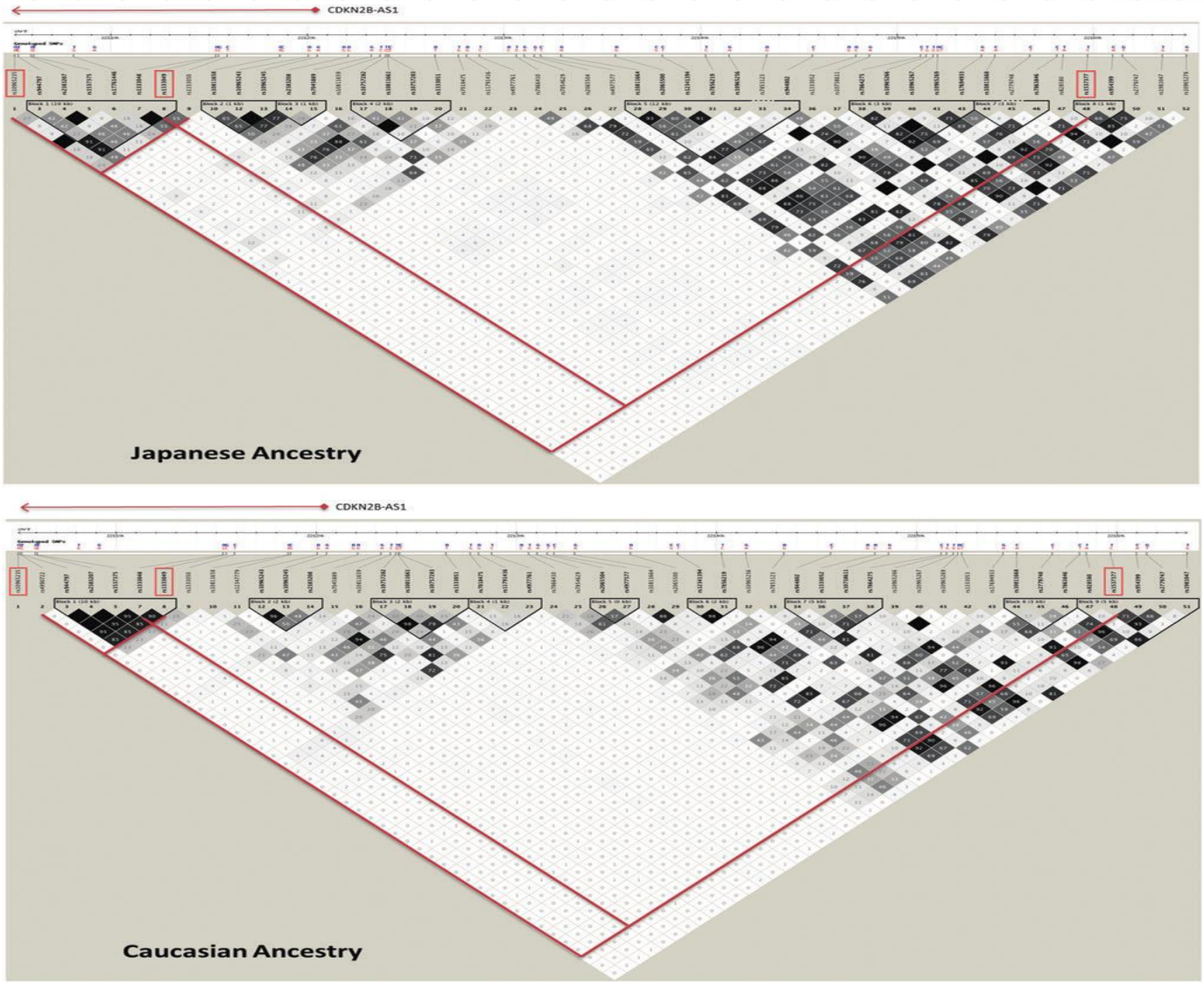
GWASs: Genome-wide association studies

Cohort	Ancestry	No. of cases	No. of stage III/IV cases[a]	No. of controls	References
OX GWAS	European (UK/USA/EU)	924	454	5190	Painter *et al.* (2011a)
QIMR GWAS	European (Australia)	2270	908	1870	Painter *et al.* (2011a)
Utah GWAS	European (USA)	2019	848	14 471	Albertsen *et al.* (2013)
NHS II replication	European (USA)	2392	No stage info	2271	Painter *et al.* (2011a)
Pagliardini replication	European (Italy)	305	220	2710	Pagliardini *et al.* (2013)
Sundqvist replication	European (Belgium)	1129	429	831	Sundqvist *et al.* (2013)
Total European ancestry		*9039*	*2859*	*27 343*	
BBJ GWAS	Japanese	1423	No stage info	1318	Uno *et al.* (2010)
BBJ replication	Japanese	1044	No stage info	4017	Uno *et al.* (2010)
Total Japanese ancestry		*2467*		*5335*	
Total		11 506	2859	32 678	

[a]rAFS III and IV disease only. OX, Oxford University; QIMR, Queensland Institute of Medical Research; NHS II, Nurses' Health Study II; BBJ, BioBank Japan.

Rahmioglu et coll, Hum Reprod update, 2014

Expression des gènes impliqués dans l'endométriose en fonction des populations



Rahmioglu et coll, Hum Reprod update, 2014

Association de SNPs (Single nucleotide polymorphisms) et risque d'endométriose

SNPs	Nearest gene	Controls	Stages III–IV		Ovarian endometriosis		Peritoneal endometriosis	
			P-values	OR (95% CI)	*P*-values	OR (95% CI)	*P*-values	OR (95% CI)
rs13394619	GREB1	general population	0.78	1.03 (0.84–1.27)	0.87	0.98 (0.80–1.21)	0.63	1.05 (0.84–1.32)
rs4141819	Intergenic	general population	0.12	1.18 (0.96–1.46)	**3.26×10^{-2}**	**1.26 (1.02–1.55)**	0.51	0.92 (0.72–1.17)
rs7739264	ID4	general population	0.53	1.07 (0.86–1.33)	0.61	1.06 (0.85–1.31)	0.29	1.14 (0.89–1.45)
rs17694933	CDKN2B-AS1	general population	**3.32×10^{-2}**	**1.25 (1.02–1.54)**	5.97×10^{-2}	1.22 (0.99–1.50)	0.46	1.09 (0.87–1.37)
rs10859871	VEZT	general population	**2.02×10^{-4}**	**1.47 (1.20–1.81)**	**1.06×10^{-4}**	**1.49 (1.22–1.83)**	**1.12×10^{-2}**	**1.33 (1.06–1.67)**

ORs are calculated for risk alleles of Table I. Data in bold are significant results.

Pagliardini et coll Hum Reprod 2015

Gènes impliqués dans l'infertilité associée à l'endométriose

Polygenic/Multifactorial

Endometriosis (OMIM 131200)	*HSD17B2*	16q23.3	109685
	CYP19A1	15q21.2	107910
	STAR	8p11.23	600617
	SF1	11q13.1	601516
	Ch region	10q26	-
	Ch region	1p36	-

Zorrilla & Yatsenko, Curr Genet Med Rep 2013

Endométriose et épigénétique

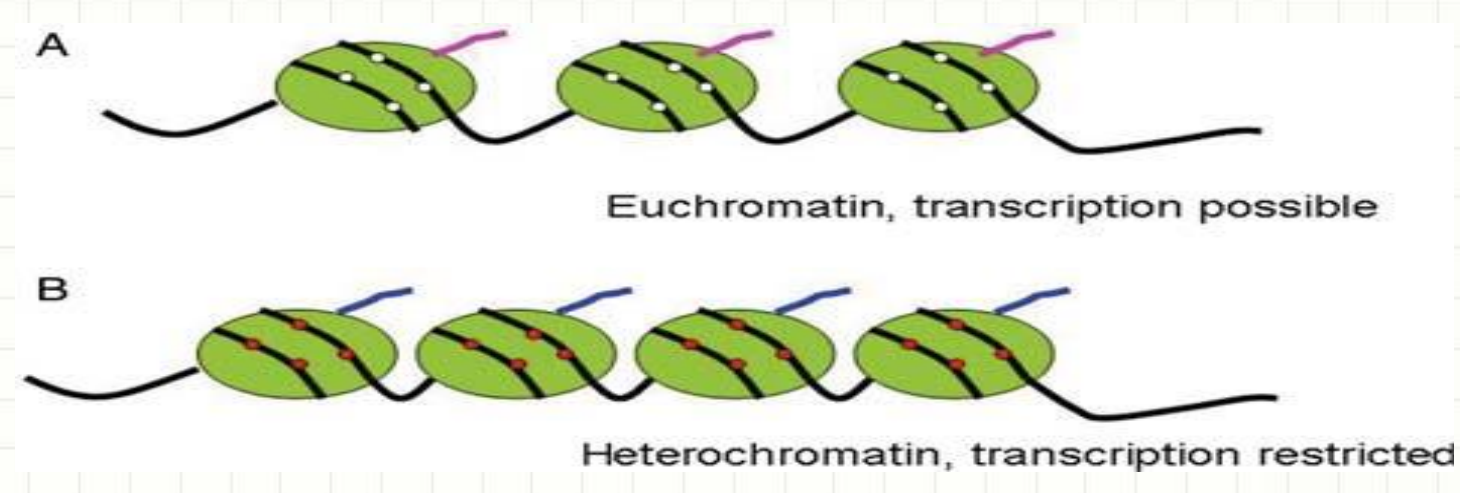


Figure 1 Schematic illustration of close interactions between DNA methylation and histone modifications.

Strands of DNA (black) are wrapped around histone octamers (olive green), collectively constituting nucleosomes. The neighboring nucleosomes are connected by linker DNAs (black). The nucleosomes, along with linker DNAs, are organized into chromatin, the building blocks of chromosomes. (**a**) Euchromatin, characterized by unmethylated CpG sites (white dots) in the promoter and characteristic chemical modifications of the histone tails (pink), is extended chromatin accessible for transcription. The gene is 'switched on'—expressed. (**b**) Heterochromatin, characterized by methylated CpG sites (red dots) in the promoter and characteristic chemical modifications of the histone tails (blue), is condensed chromatin restricted or inaccessible for transcription. The gene is 'switched off'—unexpressed.

Guo, Molecular Hum Reprod 2009

Gènes identifiés dans l'endométriose avec action épigénétique

Year of the first report	Gene name	Major finding	Reference
2005	HOXA10	Hypermethylated in eutopic endometrium	Wu *et al.* (2005), Kim *et al.* (2007), Lee *et al.* (2009)
2006	PR-B	Hypermethylated in ectopic endometrium	Wu *et al.* (2006b)
2007	Aromatase	Endometriotic cells secreted more aromatase than endometrial cells with added testosterone, yet when treated with a DMA, endometrial cells increased the secretion	Izawa *et al.* (2008)
2007	ERβ	Hypomethylated in ectopic endometrium	Xue *et al.* (2007a)
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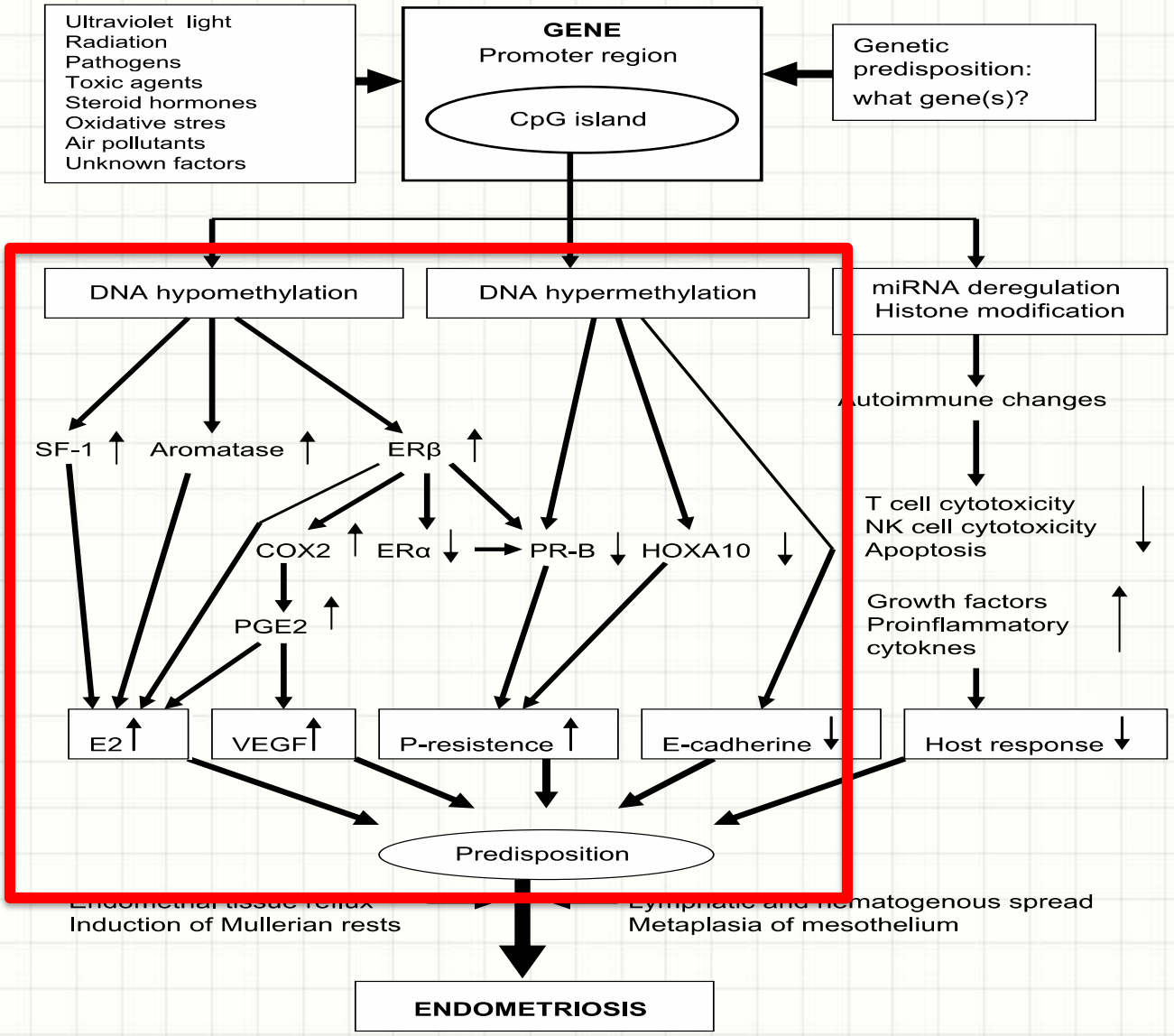
2007	E-cadherin	Methylated and inactivated in an endometriotic epithelial-like cell line, and can be demethylated and reactivated by the treatment with the HDACI, TSA	Wu *et al.* (2007a)

Epigénétique et endométriose



Kokcu J Obstet Gynaecol 2015

Rôle des miARN dans la traduction des mARN

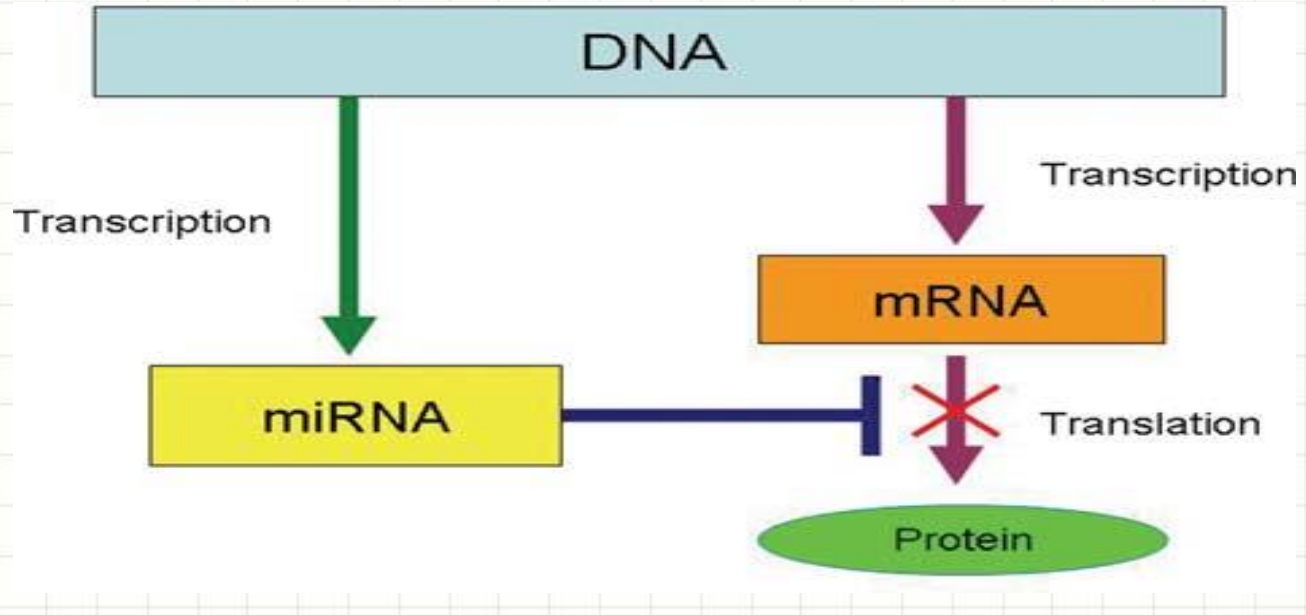


Figure 2 Schematic illustration of the canonical mechanism of protein suppression by miRNA.

MiRNAs are transcribed mainly through RNA pol II, occasionally through RNA pol III, from DNA, processed in the nucleus by Drosha to give rise to pre-miRNA, and then exported to the cytoplasm, where pre-miRNA matures into miRNA:miRNA duplex. The duplex is then recognized and cleavaged by Dicer and the resultant miRNA strand is integrated in a complex called miRISC, which by binding to target mRNA molecules inhibits translation or induces mRNA degradation. See (Bartel, 2004).

Guo, Molecular Hum Reprod 2009

Expression des miARN en fonction du type d'endométriose

	Control endometrium, *n* = 32	Eutopic endometrium, *n* = 51	Ovarian endometrioma, *n* = 51	Peritoneal endometriosis, *n* = 18	Rectovaginal endometriosis, *n* = 20
miR-16-5p	1.00 ± 0.08	1.69 ± 0.18	1.72 ± 0.27	6.12 ± 0.70$^{***, ###, \&\&\&}$	10.70 ± 2.50$^{***, ###, \&\&\&}$
miR-29c-3p	1.00 ± 0.15	0.96 ± 0.07	7.67 ± 0.79$^{***, ###}$	10.35 ± 1.43$^{***, ###}$	17.11 ± 3.16$^{***, ###, \&\&\&}$
miR-138-5p	1.00 ± 0.19	2.15 ± 0.54*	4.47 ± 0.71$^{***, ###}$	12.89 ± 2.39$^{***, ###}$	16.03 ± 2.84$^{***, ###, \&\&\&}$
miR-202-3p	1.00 ± 0.16	0.56 ± 0.07**	113.6 ± 14.30$^{***, ###}$	11.38 ± 5.03$^{*, ###}$	15.92 ± 6.15$^{*, ###, \&\&\&}$
miR-373-3p	1.00 ± 0.11	0.89 ± 0.08	1.58 ± 0.16*	2.18 ± 0.42$^{*, ##}$	1.59 ± 0.50
miR-411-5p	1.00 ± 0.14	0.90 ± 0.08	3.73 ± 0.38$^{***, ###}$	4.28 ± 0.67$^{***, ###, \&\&\&}$	7.53 ± 0.97$^{***, ###, \&\&, \phi}$
miR-411-3p	1.00 ± 0.08	0.90 ± 0.06	1.23 ± 0.13	1.32 ± 0.29*	2.39 ± 0.43$^{**, ###, \&\&, \phi}$
miR-424-5p	1.00 ± 0.14	0.71 ± 0.07*	1.07 ± 0.15$^{\#}$	1.76 ± 0.46$^{*, ##}$	1.89 ± 0.35$^{*, ###, \&}$
miR-449b-3p	1.00 ± 0.15	0.71 ± 0.10*	0.28 ± 0.05$^{***, ###}$	1.07 ± 0.52	0.47 ± 0.10$^{**, \#}$
miR-556-3p	1.00 ± 0.21	0.59 ± 0.09*	0.99 ± 0.17	0.32 ± 0.12$^{**, \&\&}$	1.35 ± 0.53
miR-636	1.00 ± 0.09	1.11 ± 0.11	0.95 ± 0.11	1.76 ± 0.36	1.78 ± 0.59
miR-935	1.00 ± 0.13	0.86 ± 0.008	1.35 ± 0.23	4.95 ± 1.68$^{*, ##, \&}$	3.15 ± 0.61$^{***, ###, \&\&}$

Data are expressed as mean ± SEM. miRNA expression is presented as fold-change relative to women without endometriosis (control endometrium = 1).
Any group versus control endometrium: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. Any group versus eutopic endometrium: $^{\#}P < 0.05$; $^{\#\#}P < 0.01$; $^{\#\#\#}P < 0.001$.
Any group versus ovarian endometrioma: $^{\&}P < 0.05$; $^{\&\&}P < 0.01$; $^{\&\&\&}P < 0.001$. Rectovaginal versus peritoneal endometriosis: $^{\phi}P < 0.05$.

Braza-Boïls et coll, Hum Reprod 2014

Endométriose et risque de cancer de l'ovaire

	Crude		Stratified only		Stratified and adjusted	
	OR (95% CI)	p value	OR (95% CI)*	p value	OR (95% CI)†	p value
Invasive	1·49 (1·34–1·65)	<0·0001	1·53 (1·37–1·70)	<0·0001	1·46 (1·31–1·63)	<0·0001
Clear-cell	3·73 (3·04–4·58)	<0·0001	3·44 (2·78–4·27)	<0·0001	3·05 (2·43–3·84)	<0·0001
Endometrioid	2·32 (1·94–2·78)	<0·0001	2·20 (1·82–2·66)	<0·0001	2·04 (1·67–2·48)	<0·0001
Mucinous	1·09 (0·76–1·58)	0·63	1·04 (0·71–1·51)	0·86	1·02 (0·69–1·50)	0·93
High-grade serous	1·11 (0·96–1·29)	0·16	1·16 (1·00–1·35)	0·056	1·13 (0·97–1·32)	0·13
Low-grade serous	2·02 (1·38–2·97)	<0·0001	2·22 (1·48–3·31)	<0·0001	2·11 (1·39–3·20)	<0·0001
Borderline	1·26 (1·05–1·50)	0·012	1·19 (0·99–1·43)	0·062	1·12 (0·93–1·35)	0·24
Mucinous	1·27 (0·97–1·67)	0·078	1·19 (0·90–1·57)	0·23	1·12 (0·84–1·48)	0·45
Serous	1·31 (1·05–1·63)	0·015	1·28 (1·02–1·61)	0·034	1·20 (0·95–1·52)	0·12

OR=odds ratio. *Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other). †Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other), and adjusted for duration of oral contraceptive use (never, <2 years, 2–4·99 years, 5–9·99 years, ≥10 years), and parity (0, 1, 2, 3, ≥4 children).

Pearce et coll., Lancet Oncol 2012

Gènes impliqués dans l'endométriose et la transformation maligne

Genes	Endometriosis susceptibility genes	Genes responsible for tumor promotion	
		Genes responsible for malignant transformation of endometriosis	Genes responsible for cancer progression
PTEN	-/+	+	+
MYC	+	ND	+
CTNNB1	-/+	ND	+
XRCC	+	ND	ND
BCL2	-/+	-/+	+
GALT	+	ND	+
GSTM1	+	ND	+
ARID1A	-	+	+
TP53	-	+	+
BRAF	-	ND	-
PIK3CA	-	+	+
ACTN4	-	+	+
TERT	-	+	+
MIB1	-	+	+
ERBB2	-	ND	+
CDKN1A	ND	ND	+
MET	-	+	+
KRAS	-	-	+

Kobayashi et coll, Molecular Med Rep 2014

Downstream uses of tissue according to different processing and storage methods.

	Cell isolation/ culture	DNA	Metabolites	Protein	RNA
Snap frozen tissue		✓	✓	✓	✓
Frozen viable cells	✓	✓	✓	✓	✓
RNAse inhibitor[a]		✓		✓	✓
Fixed tissue		✓	✓	✓	✓
Fresh tissue	✓	✓	✓	✓	✓

[a] Commercially available products: Allprotect Tissue Reagent (Qiagen); DNA/RNA Shield (Zymoresearch); ProtectRNA (Sigma-Aldrich); Ribolock (Thermoscientific); RNAlater (Qiagen); Ambion RNAsecure Reagent (Life-technologies); SUPERase-In (Life-technologies); PAXgene Tissue Containers (Qiagen).

Fassbender. Tissue collection in endometriosis research. Fertil Steril 2014.

Gènes identifiés dans l'endométriose avec action épigénétique

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2005	HOXA10	Hypermethylated in eutopic endometrium	Wu *et al.* (2005), Kim *et al.* (2007), Lee *et al.* (2009)
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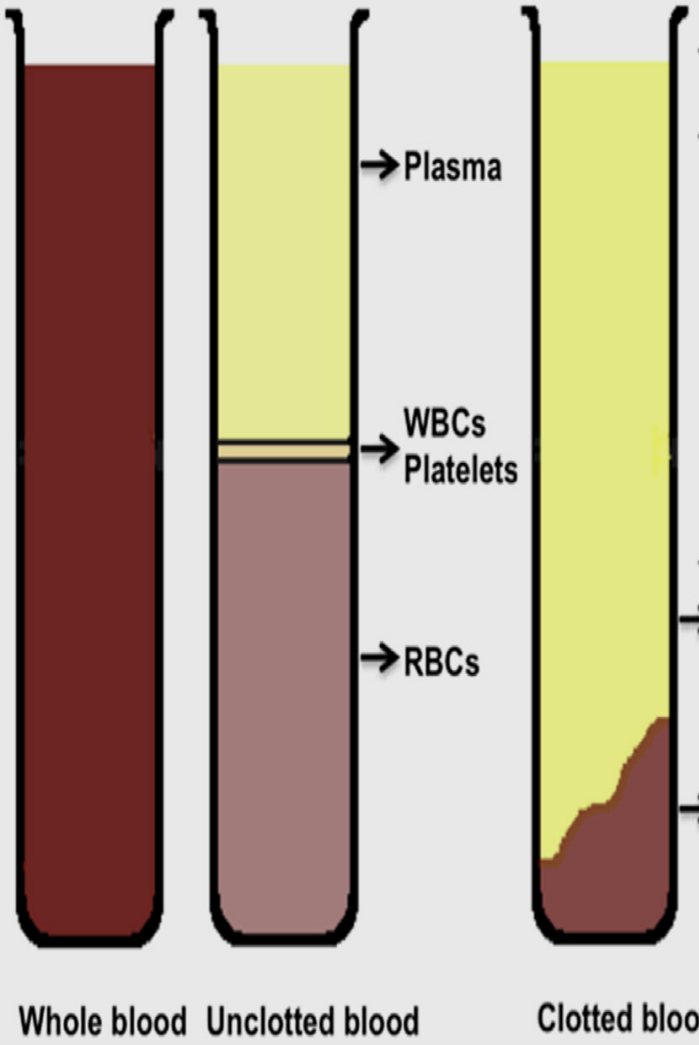
Conclusion

- Il existe des preuves de la régulation génétique et épigénétique de l'endométriose.
- La connaissance de la régulation génétique (polymorphisme) permet d'espérer des outils du diagnostic précoce de l'endométriose.
- Nouvelles thérapies non hormonales (inhibition des récepteurs EP_2 et EP_4 de PGE_2)



	DNA	RNA	Proteins	Metabolites
Whole blood	✔	✔[a]		
Plasma			✔	✔
Serum			✔	✔
WBC*	✔	✔[a]		
RBC*		✔[a]	✔	✔

[a] Using RNAlater in unclotted whole blood or WBC/RBC component.
* WBC; White blood cells, RBC; Red blood cells.

Potential uses of blood constituents in genetic, expression, protein, and metabolite analyses.

Rahmioglu. Biofluid collection in endometriosis research. Fertil Steril 2014.