A.G.E.O. E GLI ESPERTI

le nostre domande e le loro risposte

FIRENZE

25 - 26 OTTOBRE 2019

Poliabortività: come si affronta?

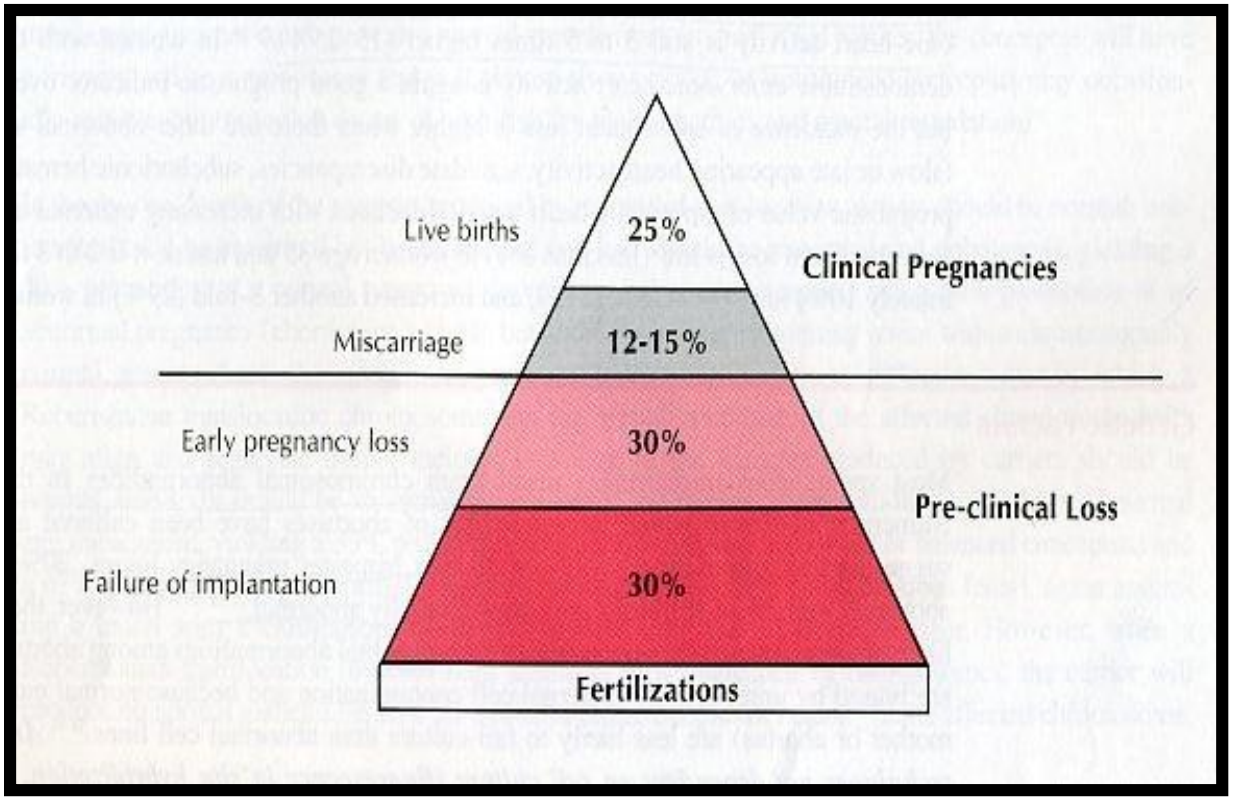
Prof. G. Mello

Dott.ssa S. Ottanelli

HUMAN PREGNANCY: A RELATIVELY INEFFICIENT PROCESS

Approximately 50-60% of conceptions fail,
the vast majority of which go unrecognized because
they occur before or within the expected next menses.

Wilcox AJ et al, 1988



RECURRENT MISCARRIAGE: DIMENSION OF THE PROBLEM

- ✓ Recurrent miscarriage affects **1%** of couples trying to conceive
- ✓ It has been estimated that **1–2%** of second-trimester pregnancies miscarry before 24 weeks of gestation

Royal College of Obstetricians & Gynaecologists

2011

RPL affects approximately **1% to 2%** of women, when defined as three consecutive pregnancy losses prior to 20 weeks

eshre SCIENCE MOVING PEOPLE MOVING SCIENCE

2017

«The exact prevalence of RPL is very difficult to estimate, as both the numbers in the numerator (experienced RPL) and the denominator (women at risk of RPL, all women at fertile age, or all women who try to get pregnant), are difficult to obtain.»

WHAT IS RECURRENT PREGNANCY LOSS?

the loss of three or more consecutive pregnancies

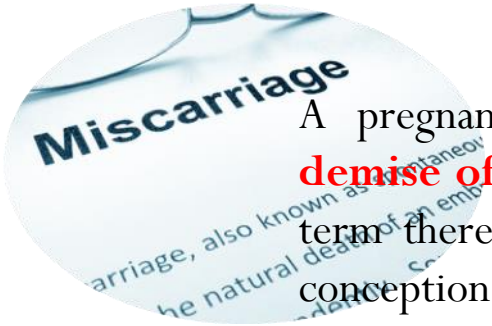
Royal College of Obstetricians & Gynaecologists

- ✓ **two or more** miscarriages.
- ✓ After three repeated miscarriages, a thorough physical exam and testing are recommended.

- ✓ the loss of **two or more** pregnancies
- ✓ It excludes ectopic pregnancy and molar pregnancy
- ✓ Implantation failure is also excluded from the definition.
- ✓ Pregnancy losses **both after spontaneous conception and after ART treatments** should be included in the definition.

November 2017

eshre SCIENCE MOVING PEOPLE MOVING SCIENCE



A pregnancy loss (miscarriage) is defined as **the spontaneous demise of a pregnancy before the fetus reaches viability.** The term therefore includes all pregnancy losses (PLs) from the time of conception **until 24 weeks of gestation**

eshre SCIENCE MOVING PEOPLE MOVING SCIENCE

Royal College of Obstetricians & Gynaecologists

WHAT IS PREGNANCY LOSS?

EARLY PREGNANCY LOSS

ACOG DEFINITION

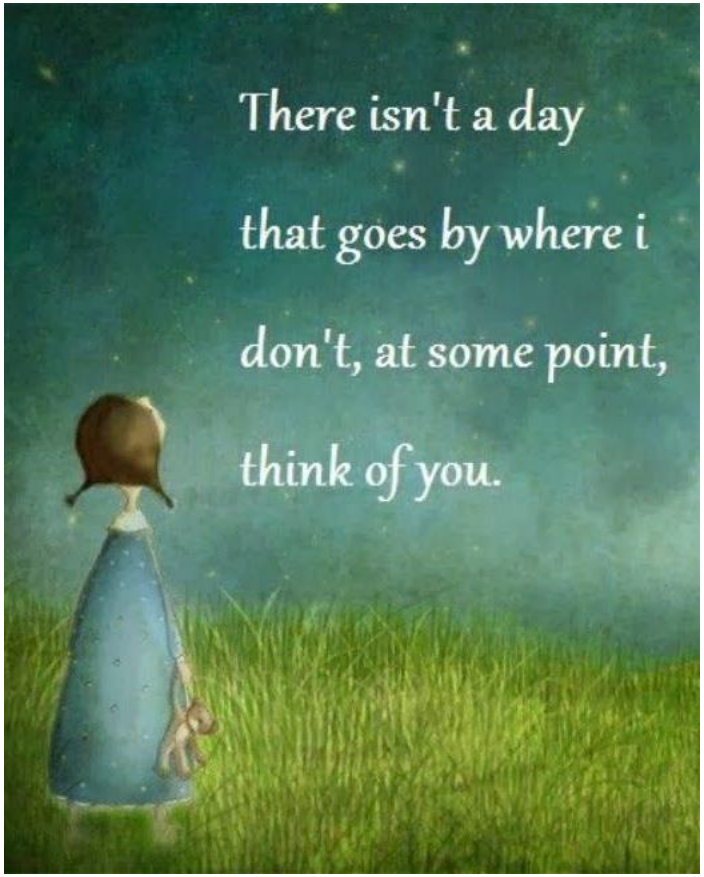
Nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without fetal heart activity within the first 12+6 weeks of gestation

ESHRE DEFINITION

"Early" Pregnancy Loss (REPL) is the loss of pregnancy **before 10 weeks of gestational age**

- ✓ Perdita di una gravidanza per parto vaginale di un feto in epoca non vitale, dopo la 12° settimana
- ✓ Perdita di una gravidanza di un feto potenzialmente vitale per morte intrauterina fetale dopo la 12° settimana

LATE PREGNANCY LOSS

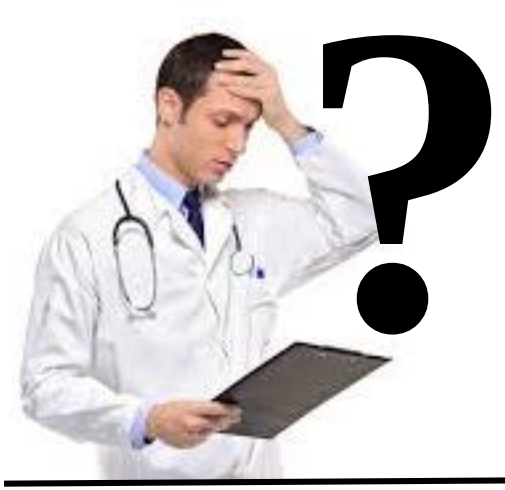


For most women and their partners, pregnancy loss represents the **loss of a baby and the hopes and plans invested in that child**

Early pregnancy loss, especially when recurrent, is an emotionally traumatic experience, similar to that associated with stillbirth or neonatal death.

Couples with pregnancy loss need empathy and understanding.

C . Lockwood, from UpToDate 2019



Recurrent pregnancy loss (RPL) is one of the most frustrating and difficult areas in reproductive medicine because the etiology is often unkown and there are few evidence-based diagnostic and treatment strategies

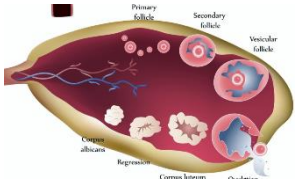
Mostra autunnale di fiori e piante al giardino dell'Orticoltura

THE WAY TO ACHIEVE A HEALTHY LIVEBORN…

POOR SPERM QUALITY
Chromosomal Abnormalities
DNA Fragmentation

Genetic disease
Environmental exposures
Varicocele

Placental disfunction/Hereditary trhombophilia
Infections
Uterine Malformations
Cervical incompetence



Ovulation **Fertilization** **Implantation** **Fetal Viability** **Healthy Liveborn**

POOR OOCYTE QUALITY
POOR OOCYTE MATURATION

Maternal Age
Genetic disease
Lifestyle

Endometrial damage
Endometritis
Asherman sindrome

Immunological factors:
APA sindrome/LES
celiac disease

Endocrinological disorders

Luteal face insufficence/PRL disorders/Thyroid Disease
Insulin resistance (PCOS/Metabolic syndrome/Obesity)

THE WAY TO ACHIEVE A HEALTHY LIVEBORN…

POOR SPERM QUALITY

Chromosomal Abnormalities

DNA Fragmentation

Genetic disease

Environmental exposures

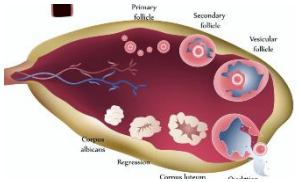
Varicocele

Placental disfunction/Hereditary trhombophilia

Infections

Uterine Malformations

Cervical incompetence



Ovulation **Fertilization** **Implantation** **Fetal Viability** **Healthy Liveborn**

POOR OOCYTE QUALITY

POOR OOCYTE MATURATION

Maternal Age
Genetic disease
Lifestyle

Endometrial damage

Endometritis

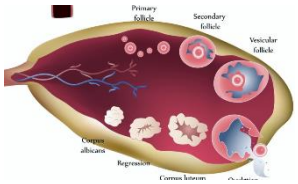
Asherman sindrome

Immunological factors:
APA sindrome/LES
celiac disease

Endocrinological disorders

Luteal face insufficence/PRL disorders/Thyroid Disease

Insulin resistance (PCOS/Metabolic syndrome/Obesity)



Maternal age

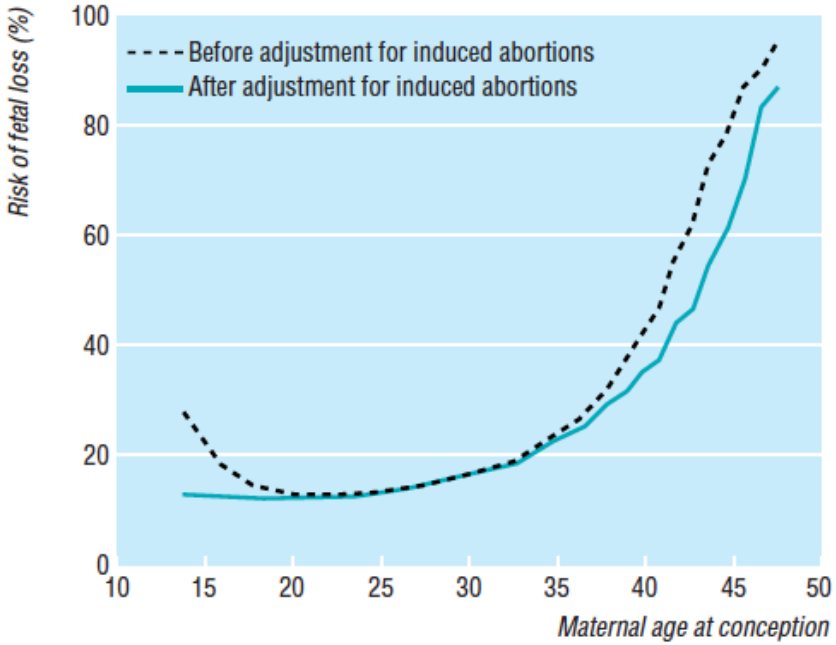


Fig 1 Risk of fetal loss from spontaneous abortion, ectopic pregnancy, and stillbirth according to maternal age at conception

Maternal age and previous number of miscarriages are two independent risk factors for a further miscarriage

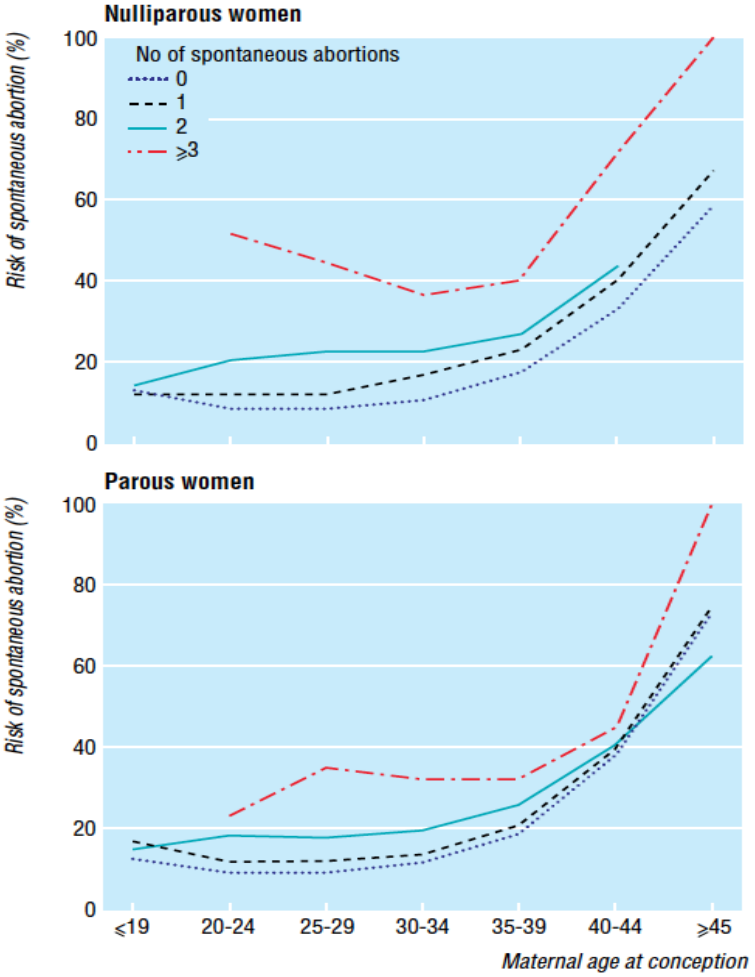
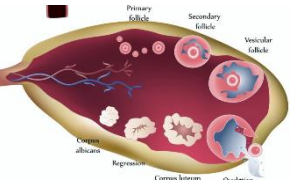


Fig 3 Risk of spontaneous abortion in nulliparous and parous women according to maternal age at conception and number of spontaneous abortions in preceding 10 years



Maternal age

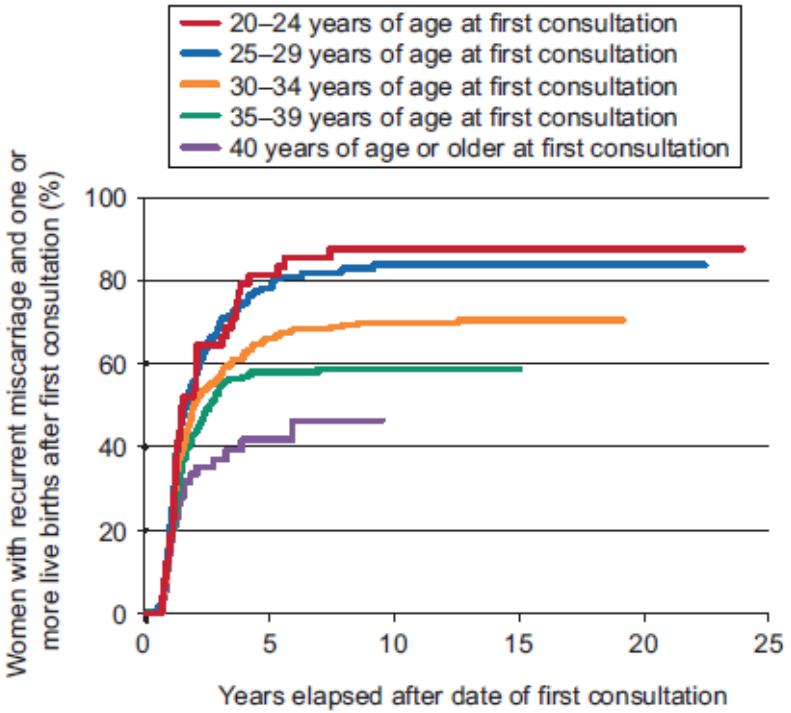


Fig. 3. Kaplan-Meier plot showing percentage of women in the recurrent miscarriage cohort who have had at least one live birth after first consultation by age at first consultation.

Lund. Recurrent Miscarriage and Prognosis for Live Birth. Obstet Gynecol 2012.

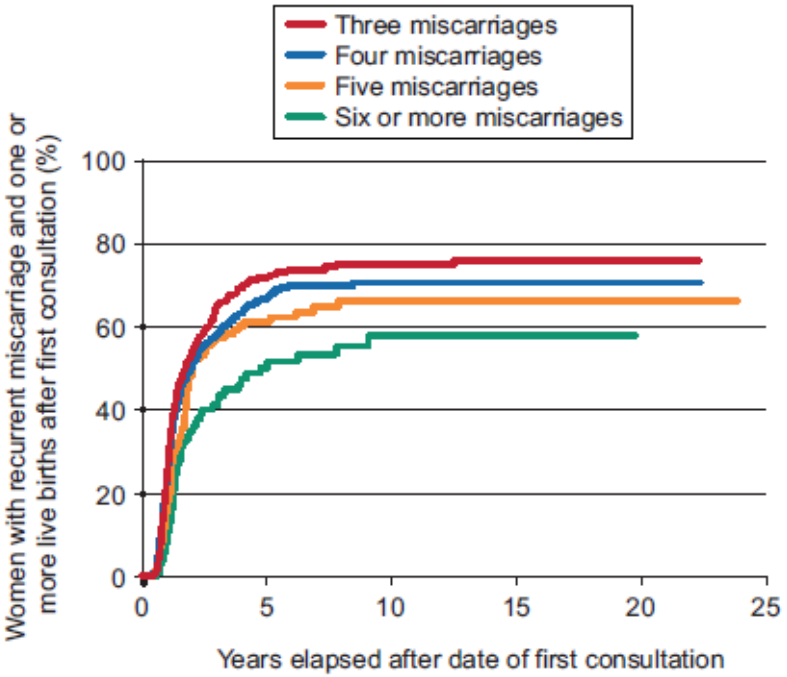
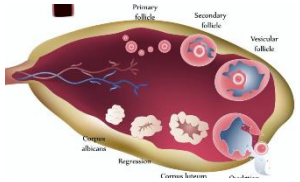


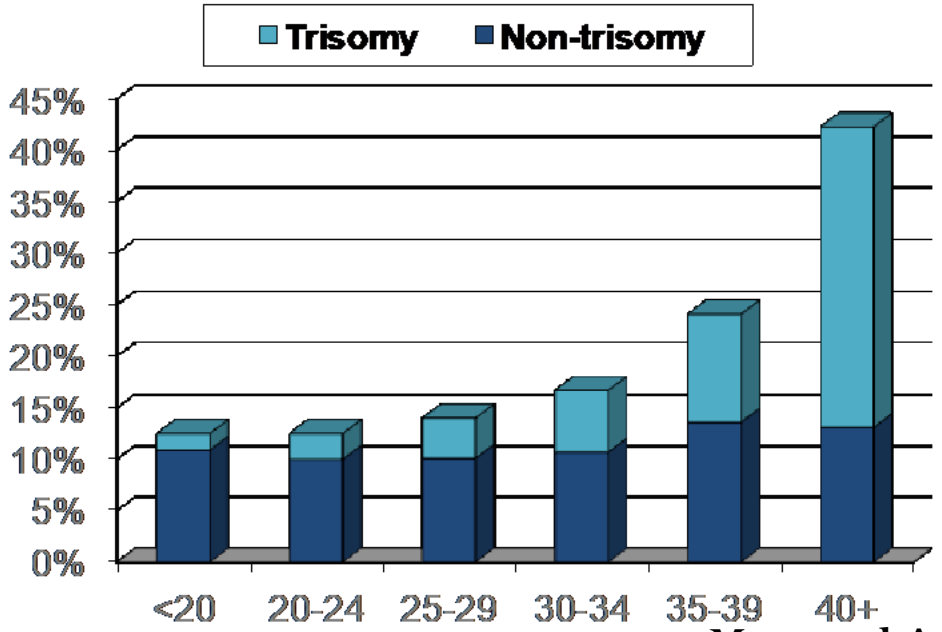
Fig. 4. Kaplan-Meier plot showing percentage of women in the recurrent miscarriage cohort who have had at least one live birth after first consultation by number of miscarriages before first consultation.

Lund. Recurrent Miscarriage and Prognosis for Live Birth. Obstet Gynecol 2012.



Maternal age/ Genetic disease

Risk of Clinical Miscarriage (≥ 6 wks)



Hassold T, Hum Genet 1985;70:11-17.

Anomalia cromosomica genitoriale strutturale bilanciata nel 2-5% delle coppie.

Genetic analysis of pregnancy tissue is not routinely recommended but it could be performed for explanatory purposes.

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

SUGGESTIONS TO IMPROVE CYTOGENETIC RESEARCH:

1) *Early intervention*
2) *Induction of uterine contractile activity with PG*
3) *Trophoblasts aspiratio and washing*
4) *Send trophoblastic sample to analyze*

WARNING!! CELLULAR COLTURE

THE WAY TO ACHIEVE A HEALTHY LIVEBORN…

POOR SPERM QUALITY

Chromosomal Abnormalities

DNA Fragmentation

Genetic disease

Environmental exposures

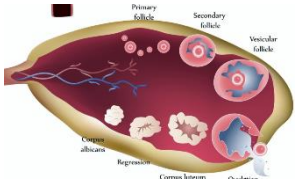
Varicocele

Placental disfunction/Hereditary trhombophilia

Infections

Uterine Malformations

Cervical incompetence



Ovulation **Fertilization** **Implantation** **Fetal Viability** **Healthy Liveborn**

POOR OOCYTE QUALITY

POOR OOCYTE MATURATION

Maternal Age
Genetic disease
Lifestyle

Endometrial damage

Endometritis

Asherman sindrome

Immunological factors:

APA sindrome/LES

celiac disease

Endocrinological disorders

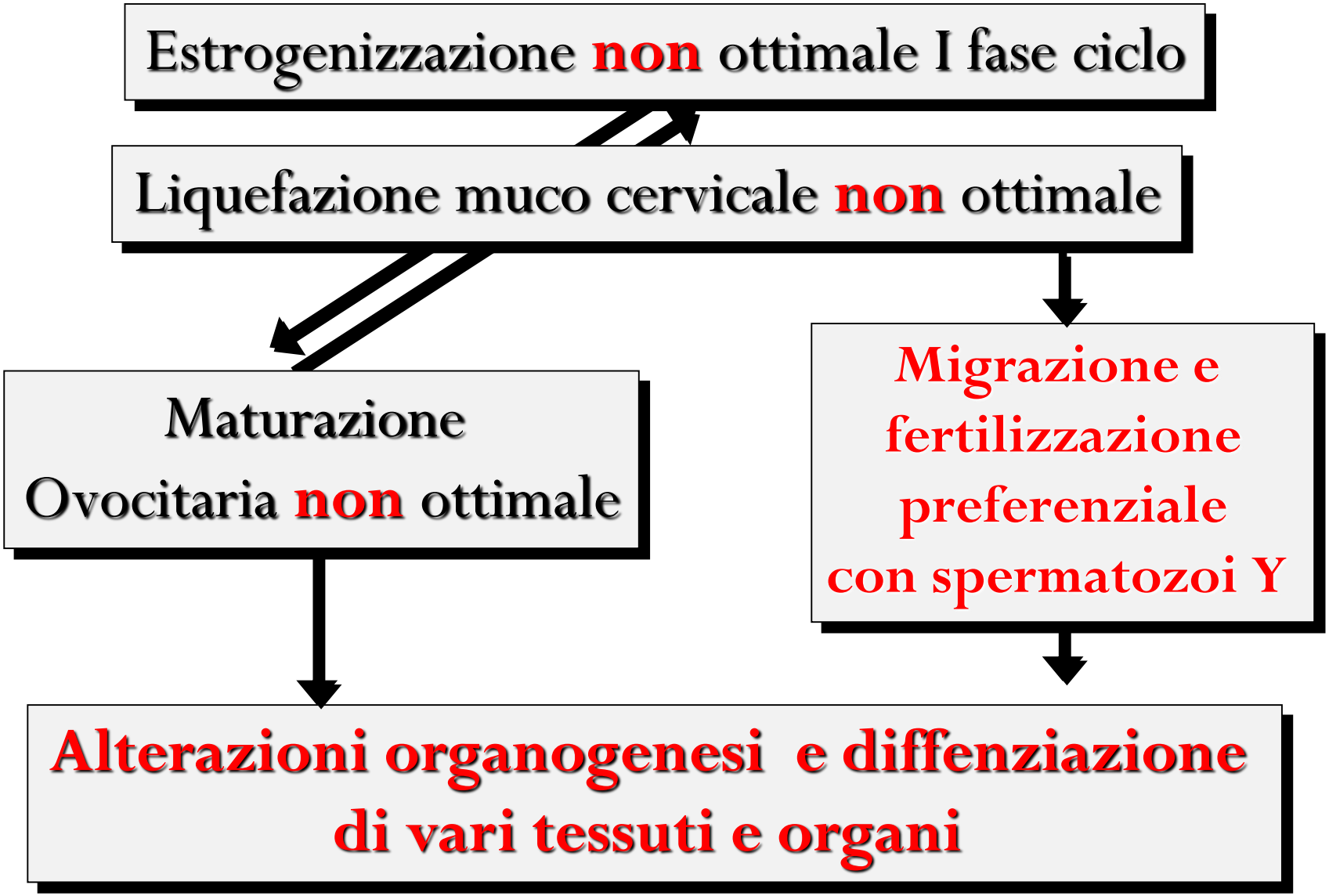
Luteal face insufficence/PRL disorders/Thyroid Disease

Insulin resistance (PCOS/Metabolic syndrome/Obesity)

MATURAZIONE OVOCITARIA FISIOLOGICA

PH Jongbloet, 2004

MATURAZIONE OVOCITARIA PATOLOGICA



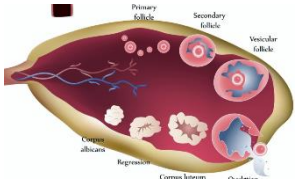
PH Jongbloet, 2004

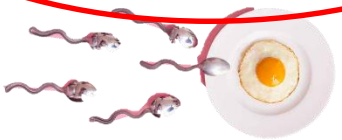
THE WAY TO ACHIEVE A HEALTHY LIVEBORN…

POOR SPERM QUALITY
Chromosomal Abnormalities
DNA Fragmentation

Genetic disease
Environmental exposures
Varicocele

Placental disfunction/Hereditary trhombophilia
Infections
Uterine Malformations
Cervical incompetence





Ovulation **Fertilization** **Implantation** **Fetal Viability** **Healthy Liveborn**

POOR OOCYTE QUALITY
POOR OOCYTE MATURATION

Maternal Age
Genetic disease
Lifestyle

Endometrial damage
Endometritis
Asherman sindrome

Immunological factors:
APA sindrome/LES
celiac disease

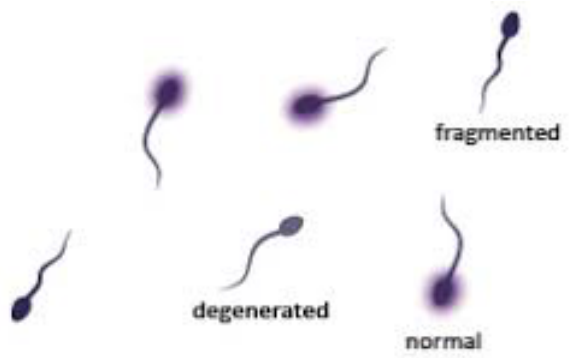
Endocrinological disorders

Luteal face insufficence/PRL disorders/Thyroid Disease
Insulin resistance (PCOS/Metabolic syndrome/Obesity)

The male contribution to recurrent pregnancy loss

Transl Androl Urol 2018;7(Suppl 3):S317-S327

With the information we currently have, ***testing for sperm chromosomal abnormalities and DNA fragmentation*** *appears to be a reasonable option for male partners of women with unexplained RPL*



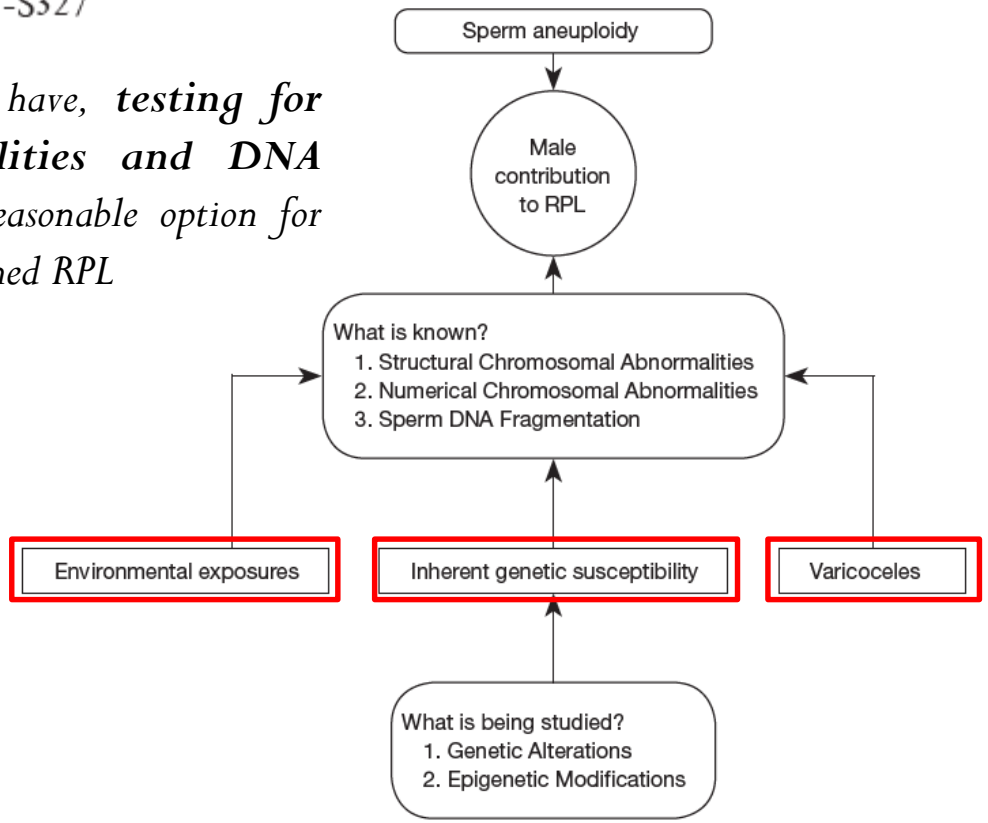


Table 5 Modifiable factors in the treatment of oxidative stress causing DNA fragmentation.

Medical factor	*Lifestyle change*	*Dietary change*	*Supplement*
Treatment of leukocytospermia Surgical repair of varicocele	Smoking cessation Avoid xenobiotic sources of reactive oxygen species Avoid heavy/toxic metals Avoid testicular heat Avoid testicular mobile phone radiation	Healthy diet Increase in fruit/vegetables and sources of antioxidants Weight loss	Vitamin C Vitamin E Mixed antioxidants?

In summary, **advanced paternal age** appears to be associated with a **modest increase in the risk of miscarriage**; this risk is lower than that observed with advanced maternal age and seems to occur at an older age than in females (over age 40 in males versus over age 30 in females), but there is no age threshold after which men cannot father offspring.

Practice Committee of the American Society for Reproductive Medicine. Fertil Steril 2002

The oocyte and the hormonal conditions that guarantee its optimum maturation play an important part in the causation of unfavorable pregnancy outcomes, as proven in animal experiments and circumstantially shown in human being

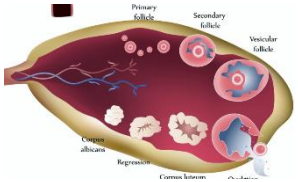
PH Jongbloet, PCM Pasker-de Jong, 2002

THE WAY TO ACHIEVE A HEALTHY LIVEBORN…

POOR SPERM QUALITY
Chromosomal Abnormalities
DNA Fragmentation

Genetic disease
Environmental exposures
Varicocele

Placental disfunction/Hereditary trhombophilia
Infections
Uterine Malformations
Cervical incompetence



Ovulation **Fertilization** **Implantation** **Fetal Viability** **Healthy Liveborn**

POOR OOCYTE QUALITY
POOR OOCYTE MATURATION

Maternal Age
Genetic disease
Lifestyle

Endometrial damage
Endometritis
Asherman sindrome

Immunological factors:
APA sindrome/LES
celiac disease

Endocrinological disorders

Luteal face insufficence/PRL disorders/Thyroid Disease
Insulin resistance (PCOS/Metabolic syndrome/Obesity)

LUTEAL PHASE INSUFFICIENCY

"a condition of insufficient progesterone exposure to maintain a regular secretory endometrium and is allowed for normal embryo implantation and growth"

Palomba S, Journal of Ovarian Research 2015

Luteal phase insufficiency can be caused by several endocrinopathies, including stress, PCOS, and prolactin disorders

Ke RW Obstet Gynecol Clin North Am. 2014

	Association	Contributing factor	Prognosis	Treatment
Luteal phase insufficiency testing*	Inconsistent	No data	No	possible

* *midluteal progesterone or endometrial biopsy*

Luteal phase insufficiency testing is not recommended in women with RPL.	Strong	⊕⊕◯◯

Possibile ruolo della T° basale?

PROLACTIN DISORDERS

adequate circulating concentration of prolactin is essential to maintain corpus luteum function

Gafvels et al. 1992; Oda et al. 1991; Garzia et al. 2004

GnRH release
HCG-induced ovulation

negative regulatory function on endometrial decidualisation

Milenkovic´ et al. 1994; Liu et al. 1997; Eyal et al. 2007

Prolactin disorders are possibly associated with PCOS, luteal phase deficiency, stress and obesity, which further complicates studies attempting to find a direct link between prolactin and RPL.

PROLACTIN DISORDERS

In women with RPL and hyperprolactinemia, bromocriptine treatment normalizes serum prolactin levels and it could be effective for increasing the chance of a live birth.

Results of randomized bromocriptine treatment trials for hyperprolactinemic and occult hyperprolactinemic recurrent miscarriage.

Group	No. of conceptions	No. (%) of live births	No. (%) of miscarriages
Treated with bromocriptine (n = 24)	21	18 (85.7%)	3 (14.3%)*
Not treated with bromocriptine (n = 22)	21	11 (52.4%)	10 (47.6%)

* P <.005 by Fisher's exact probability test (versus the group not treated with bromocriptine).

REPRODUCTIVE ENDOCRINOLOGY

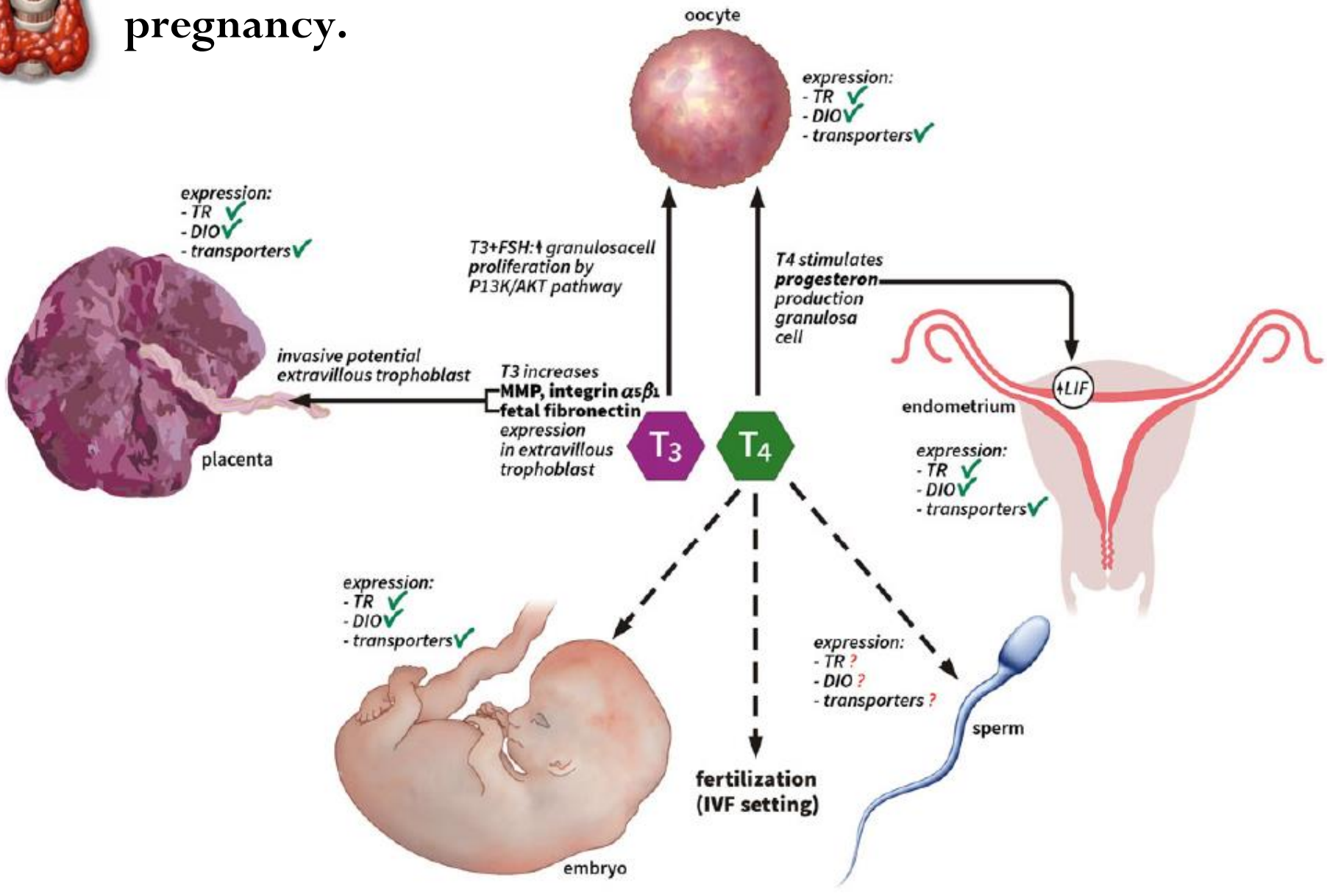
Hirahara et al, Fertil Steril 1998

Bromocriptine treatment can be considered in women with RPL and hyperprolactinemia to increase live birth rate.

Conditional ⊕OOO

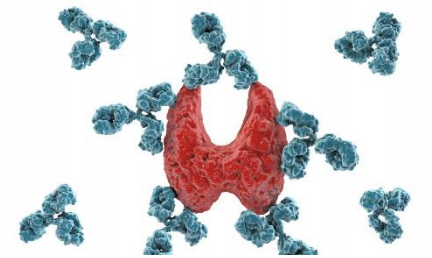
eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Role for thyroid hormone in reproduction and early pregnancy.



R. Vissenberg[1†*], Human Reproduction Update, Vol.0, No.0 pp. 1–10, 2015

Thyroid auto immunity (anti TPO) and RPL

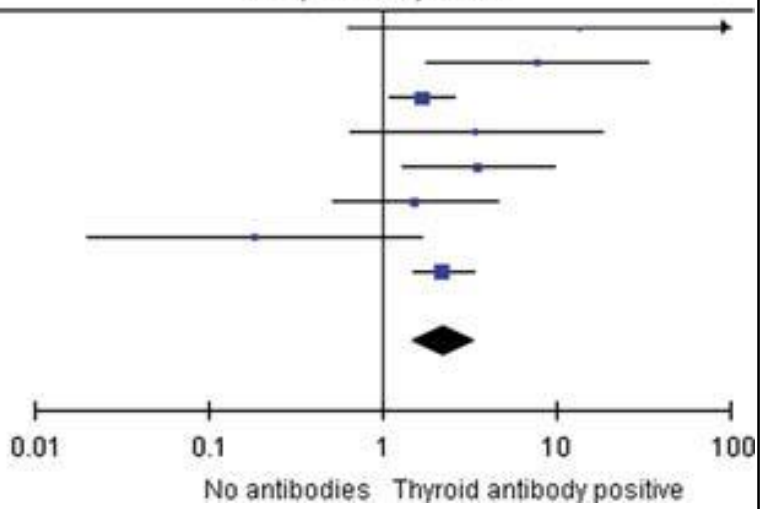


A CLEAR ASSOCIATION BETWEEN THYROID AUTO IMMUNITY AND RPL HAS BEEN FOUND.

Study	Patients Events	Total	Controls Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Roberts 1996	4	4	7	18	1.9%	13.80 [0.65, 295.25]
Bussen 1997	8	11	14	55	7.3%	7.81 [1.82, 33.59]
Kutteh 1999b	158	187	542	713	28.1%	1.72 [1.12, 2.65]
Dendrinos 2000	11	13	19	31	5.8%	3.47 [0.65, 18.47]
Mecacci 2000	11	21	18	77	12.7%	3.61 [1.32, 9.86]
Shoenfeld 2006	8	14	97	211	11.4%	1.57 [0.53, 4.67]
Bellver 2008	1	6	29	56	3.6%	0.19 [0.02, 1.70]
Iravani 2008	157	191	484	719	29.1%	2.24 [1.50, 3.35]
Total (95% CI)		**447**		**1880**	**100.0%**	**2.26 [1.46, 3.50]**
Total events	358		1210			

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 11.85$, df = 7 (P = 0.11); $I^2 = 41\%$

Test for overall effect: Z = 3.65 (P = 0.0003)



studies comparing euthyroid thyroid antibody positive patients with euthyroid antibody negative controls according to the risk of recurrent miscarriage.

Emmy van den Boogaard [1],

Human Reproduction Update, Vol.17, No.5 pp. 605–619, 2011

The presence of TPO-Ab negatively influences folliculogenesis, spermatogenesis, fertilization rates, embryo quality and pregnancy rates, but no data are available on the potential mechanisms.

Thyroid auto immunity (anti TSH-R) and RPL

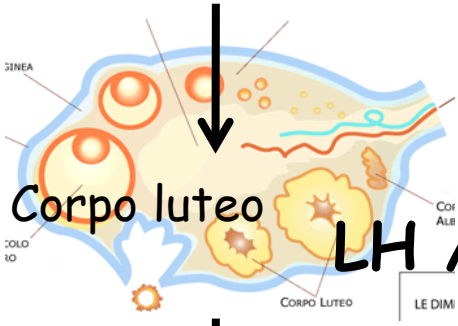
ANTI-TSH r AUTOANTIBODIES AND PREGNANCY FAILURE
THE CORPUS LUTEUM HYPOTHESIS

GLYCOPROTEIN HORMONE RECEPTORS

FSH-R, TSH-R, LH/CG-R

significant degree of sequence homology and structural similarity !

TSH-R Ab



↓progesterone

Pregnancy loss

Konstantinos A Toulis Medical Hypotheses 73 (2009)

Subclinical hypothyroidism (SCH) and RPL

Increased Pregnancy Loss Rate in Thyroid Antibody Negative Women with TSH Levels between 2.5 and 5.0 in the First Trimester of Pregnancy

Roberto Negro, J Clin Endocrinol Metab, September 2010,

YES

Impact of subclinical hypothyroidism in women with recurrent early pregnancy loss

Lia A. Bernardi, M.D.,[a]

Fertility and Sterility® / NOVEMBER 2013

NO

Is subclinical hypothyroidism associated with lower live birth rates in women who have experienced unexplained recurrent miscarriage?

Myrthe M van Dijk

Reproductive BioMedicine Online (2016)

Thyroid disease and RPL

	Association	Contributing factor	Prognosis	Treatment
Hypothyroidism	Only sporadic PL	Only for sporadic PL	Yes	Supplementation of Levothyroxine
Subclinical hypothyroidism	Yes	Yes	No clear effect as of yet.	Unknown if effective
Hyperthyroidism	No	No	No clear effect as of yet.	Yes: Propylthiouracil
TPO-antibodies	Yes	Yes	Yes	Need for treatment studies
TG antibodies	No	Mostly detected combined with TPO antibodies	Yes	Need for treatment studies

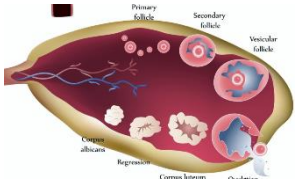
Thyroid screening (TSH and TPO antibodies) is recommended in women with RPL	Strong	⊕⊕⊕○

THE WAY TO ACHIEVE A HEALTHY LIVEBORN…

POOR SPERM QUALITY
Chromosomal Abnormalities
DNA Fragmentation

Genetic disease
Environmental exposures
Varicocele

Placental disfunction/Hereditary trhombophilia
Infections
Uterine Malformations
Cervical incompetence



Ovulation **Fertilization** **Implantation** **Fetal Viability** **Healthy Liveborn**

POOR OOCYTE QUALITY
POOR OOCYTE MATURATION

Maternal Age
Genetic disease
Lifestyle

Endometrial damage
Endometritis
Asherman sindrome

Immunological factors:
APA sindrome/LES
celiac disease

Endocrinological disorders

Luteal face insufficence/PRL disorders/Thyroid Disease
Insulin resistance (PCOS/Metabolic syndrome/Obesity)

PREGNANCY : A MILD INFLAMMATORY STATE

In women with RPL, signifi

the Th1 cytokine IFN-gan

When peripheral blood m

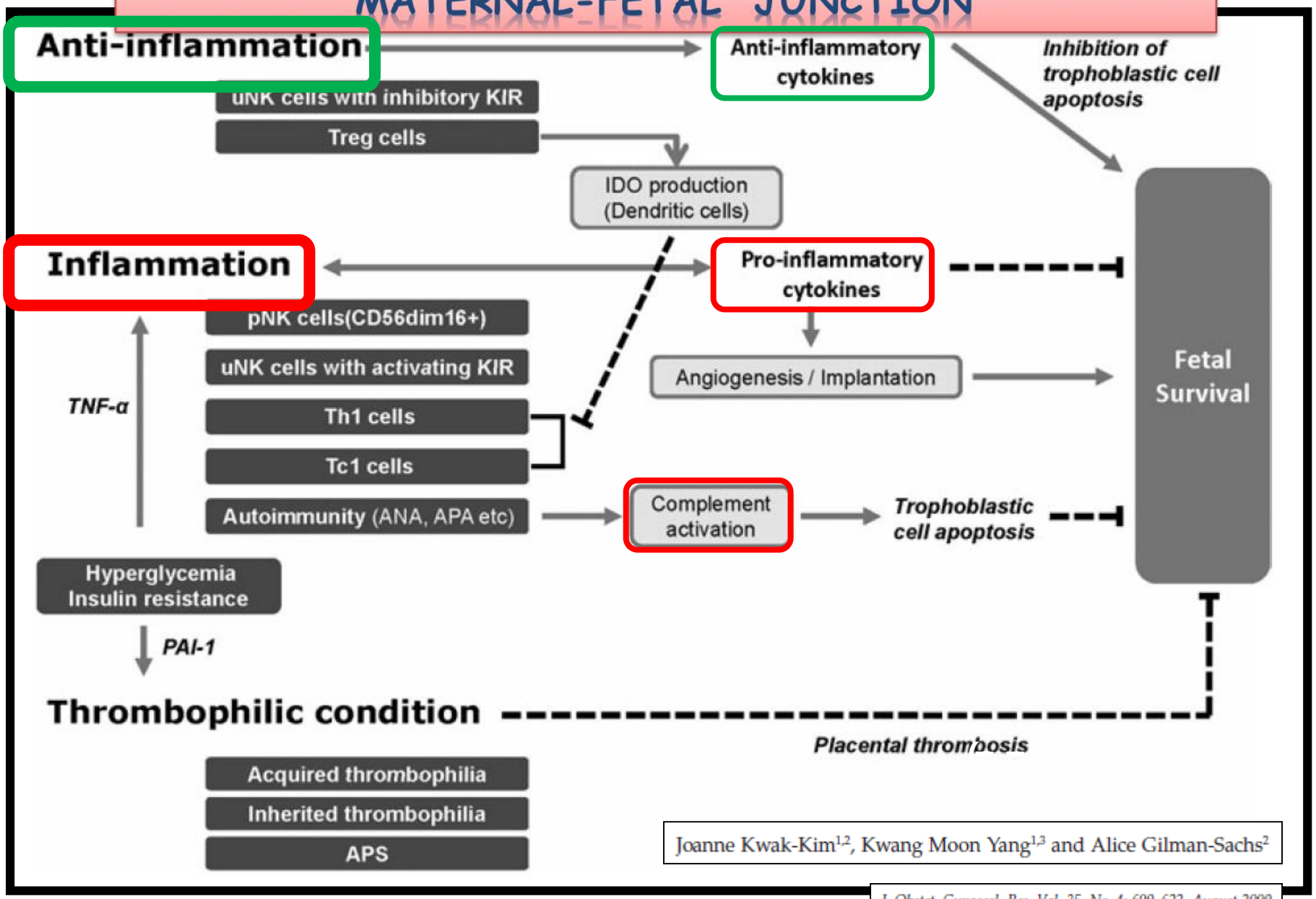
stimulated TNF-alfa, IFN-gan

secretion was **significantly**

normal controls.

Recurrent pregnancy loss: A disease of inflammation and coagulation, Kwak-Kim, 2009

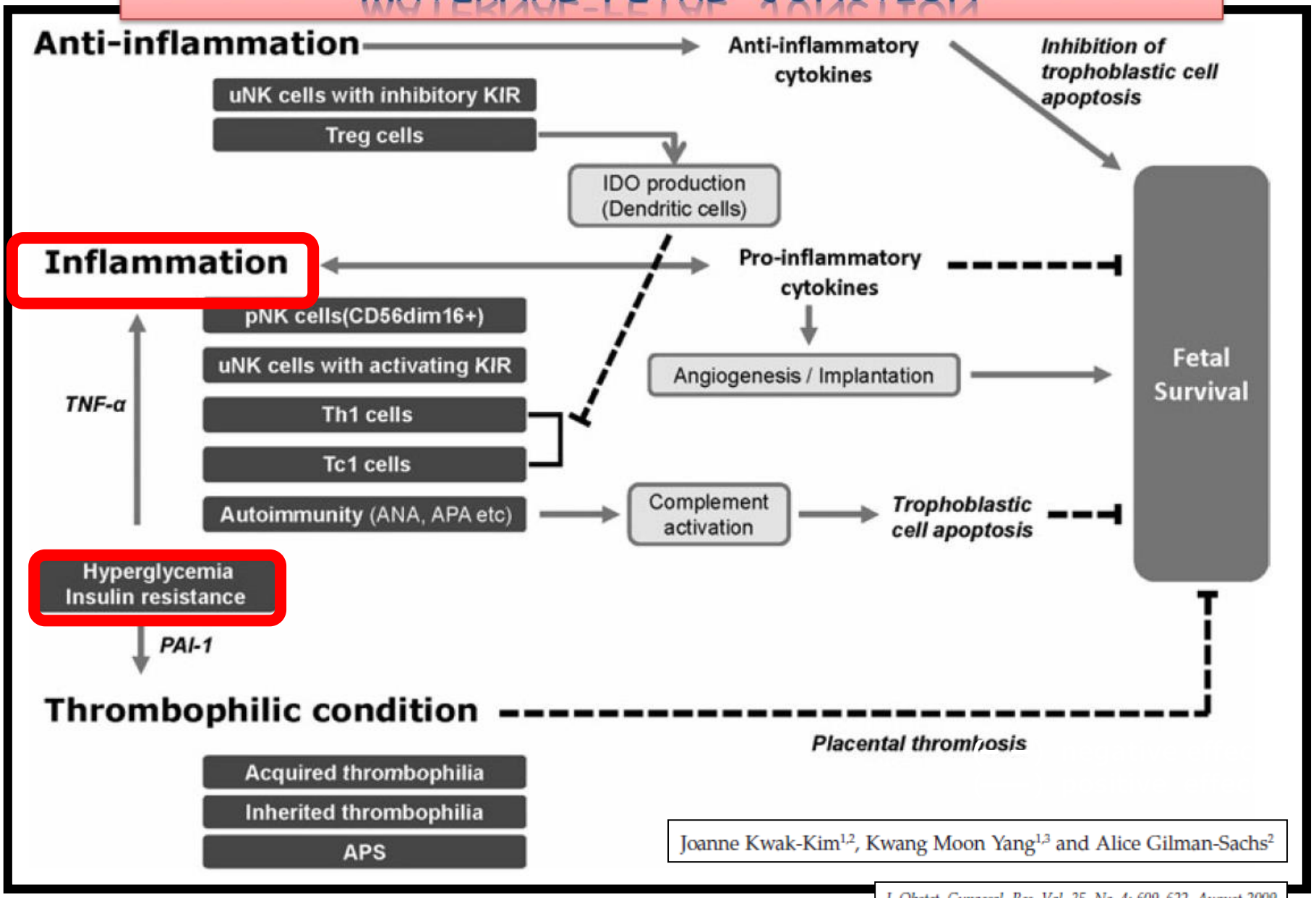
INFLAMMATORY-THROMBOTIC PROCESS AT MATERNAL-FETAL JUNCTION



Joanne Kwak-Kim[1,2], Kwang Moon Yang[1,3] and Alice Gilman-Sachs[2]

J. Obstet. Gynaecol. Res. Vol. 35, No. 4: 609–622, August 2009

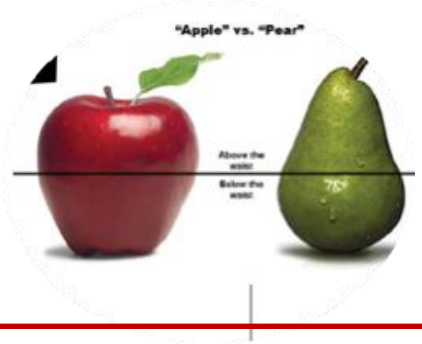
INFLAMMATORY-THROMBOTIC PROCESS AT MATERNAL-FETAL JUNCTION



Joanne Kwak-Kim[1,2], Kwang Moon Yang[1,3] and Alice Gilman-Sachs[2]

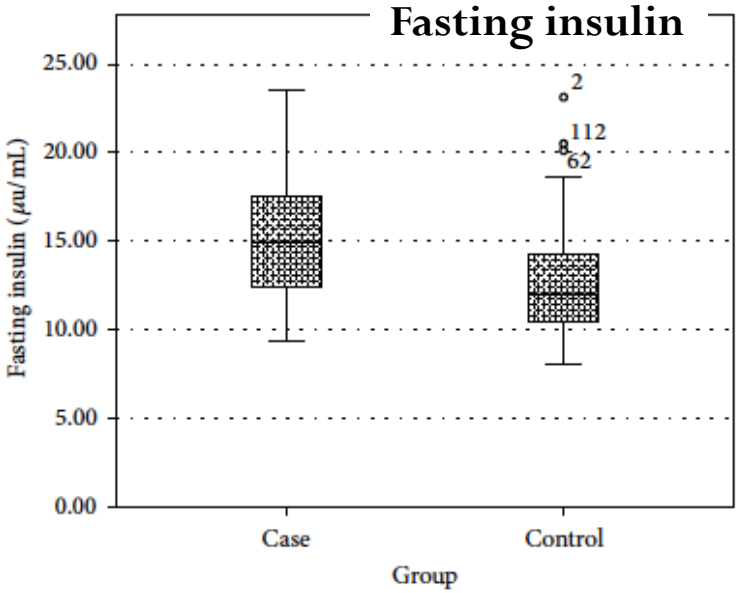
J. Obstet. Gynaecol. Res. Vol. 35, No. 4: 609–622, August 2009

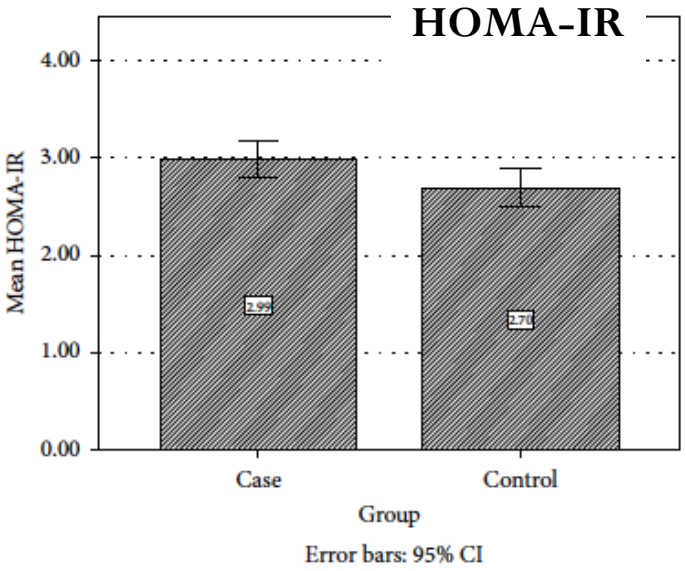
INSULIN RESISTANCE and RPL



High Fasting Insulin Levels and Insulin Resistance May Be Linked to Idiopathic Recurrent Pregnancy Loss: A Case-Control Study

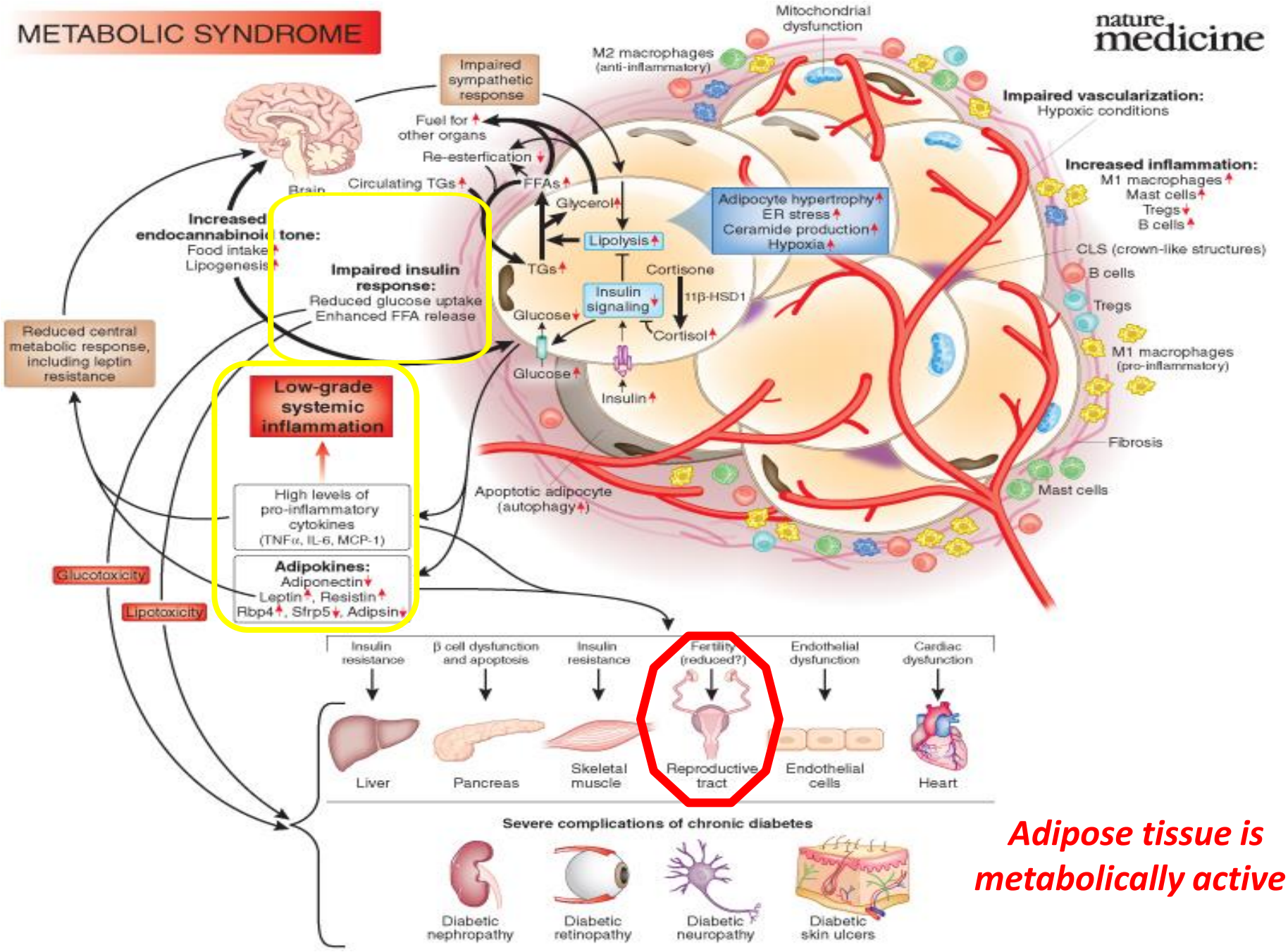
118 women, 65 idiopathic recurrent pregnancy loss.





Current study showed that, in women with idiopathic recurrent pregnancy loss, FI and IR are higher than in women without abortion
but further more comprehensive studies are needed in the future

International Journal of Endocrinology
Volume 2013, Article ID 576926, 4 pages



Adipose tissue is metabolically active!

PCOS: hormonal aberrations in endometrium

Hyperinsulinism

Hyperandrogenism

Anovulation

++AR

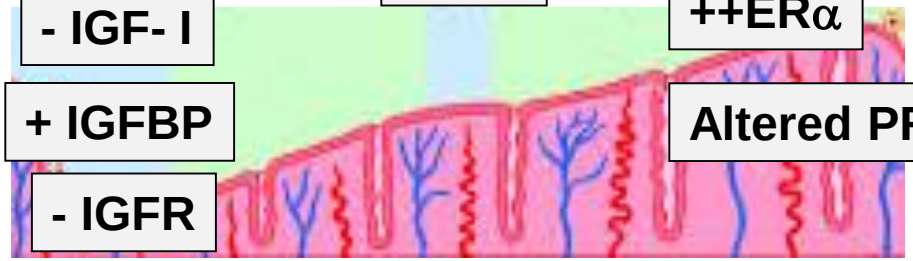
- IGF- I

+ IGFBP

- IGFR

++ERα

Altered PR expression



endometrium

Endometrial dysfunction

decreased expression of glycodelin and β3 integrin

Impaired decidualization

Impaired trophoblast invasion

Obstetric complications

Cakmak and Taylor, Hum Reprod Update, 2011

Makieva S, Hum Reprod Update, 2014

Piltonen TT, Hum Reprod , 2015

OBESITA' E ABORTO SPONTANEO

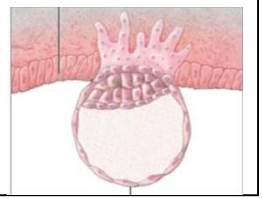
OBESITA'- INSULINO RESISTENZA

↑ ANDROGENI ↑ PAI

IPERINSULINEMIA

↓ Glycodelina
↓ IGFBP-1

AMBIENTE ENDOMETRIALE SFAVOREVOLE ALL'IMPIANTO.



OBESITA' E ABORTO SPONTANEO

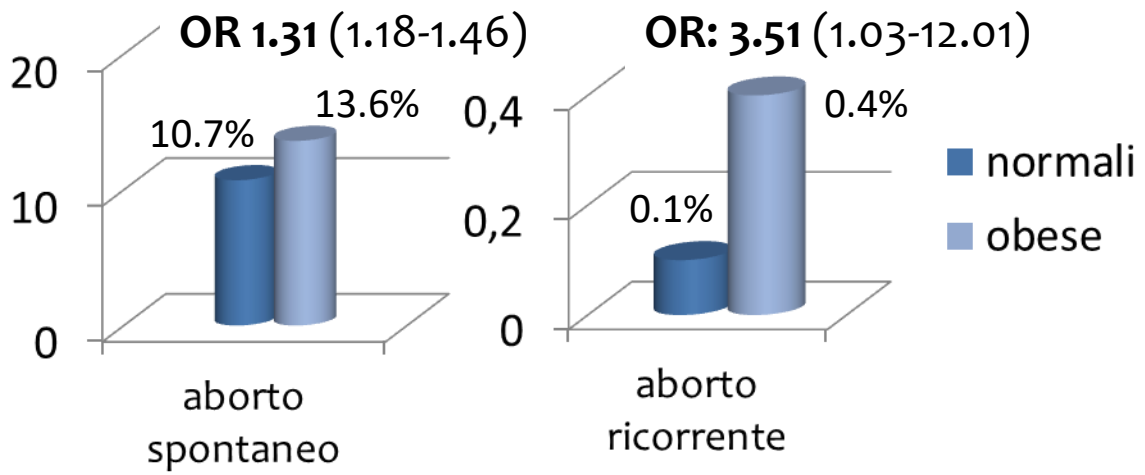
Le donne con **BMI > 25 kg/m2** hanno un rischio aumentato di aborto, indipendentemente dal tipo di concepimento **OR 1.67** (1.25–2.25).

Metwally M. Fertil Steril 2008

Anormalità dell'ovocita

Difetto di recettività endometrio ?

Aneuploidie



6 studi, 28.538 donne, concepimento spontaneo

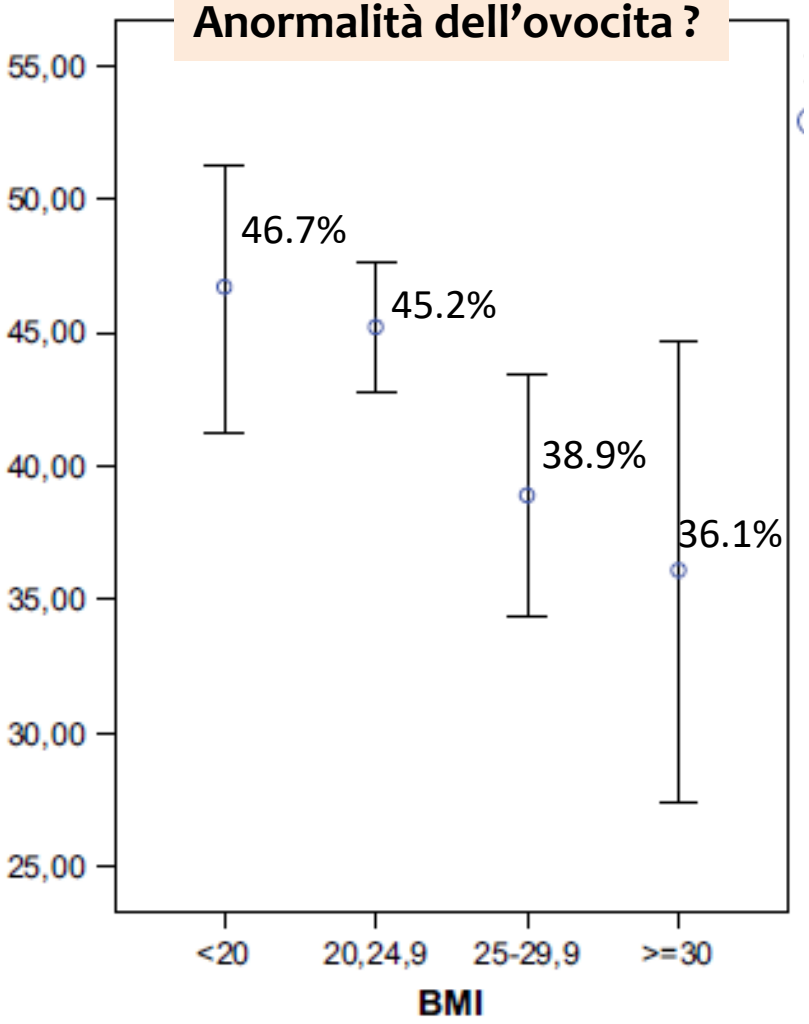
Semin Reprod Med 2011; 29(6): 507-513

OBESITA' E ABORTO SPONTANEO

EARLY PREGNANCY

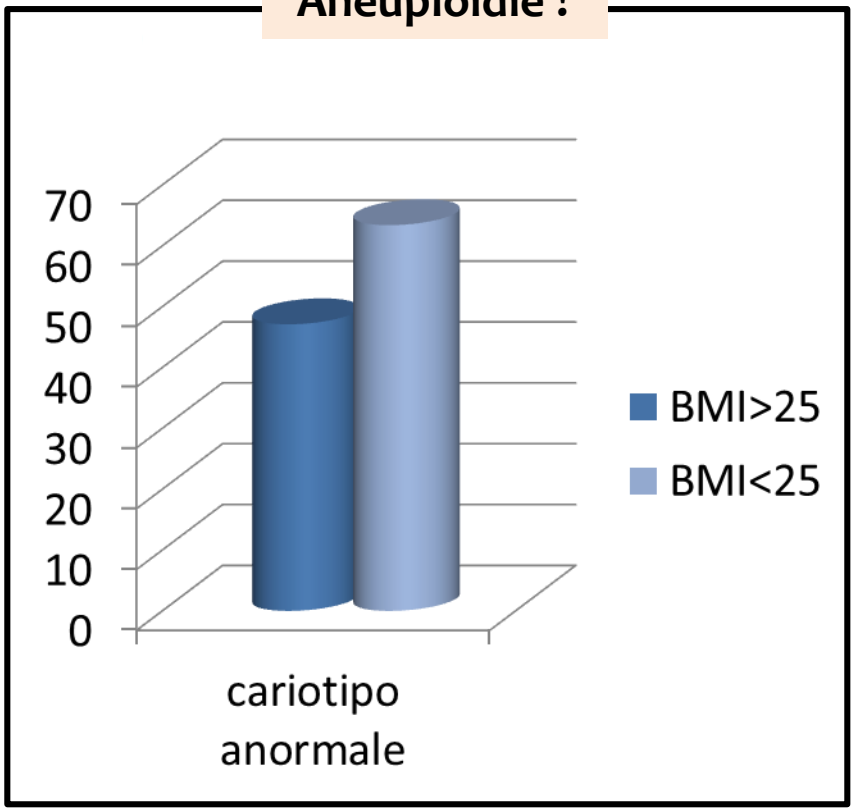
Ongoing pregnancy rate per cycle (%) in each body mass index (BMI) group. CI: confidence interval.

Anormalità dell'ovocita ?



Bellver et al. *Fertil Steril 2007.*

Aneuploidie ?



"elevated maternal BMI is associated with an increase in the miscarriage rate of genetically normal embryos"

V. Landres Human Reproduction, 2010

METFORMINA IN PCOS/INSULINO RESISTENZA

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Begum et al. 2009	2	29	3	33	7.6%	0.74 [0.11, 4.77]
Jakubowicz et al. 2002	8	68	6	31	21.1%	0.56 [0.17, 1.77]
Nawaz et al. 2008	2	45	5	26	17.6%	0.20 [0.03, 1.09]
Salvesen et al. 2007	0	18	3	22	9.0%	0.15 [0.01, 3.12]
Vanky et al. 2004	0	17	5	21	14.0%	0.09 [0.00, 1.67]
Vanky et al. 2010	5	135	11	135	30.8%	0.43 [0.15, 1.28]
Total (95% CI)		**312**		**268**	**100.0%**	**0.37 [0.20, 0.68]**
Total events	17		33			

Heterogeneity: Chi² = 2.90, df = 5 (P = 0.72); I² = 0%
Test for overall effect: Z = 3.17 (P = 0.002)

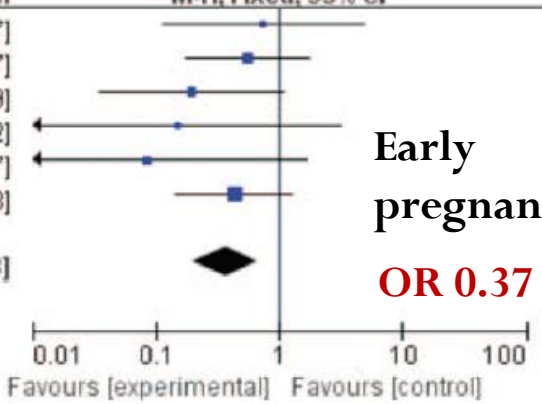


Figure 3. Meta-analysis of data about preterm labor from 6 studies using a fixed-effect model. CI=confidence interval, OR=odds ratio.

Early pregnancy loss

OR 0.37

Xian-Ling Zeng, Medicine 2016

November 2017

In patients with PCOS, metformin was found to significantly reduce the rate of miscarriage

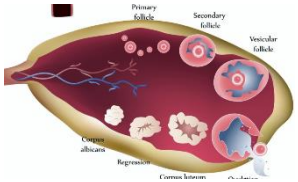
Based on these results, it could be suggested that treatment with metformin increases the chance of a live birth in women with PCOS and a history of recurrent pregnancy loss. However, there are no studies focusing on women with RPL and PCOS.

THE WAY TO ACHIEVE A HEALTHY LIVEBORN…

POOR SPERM QUALITY
Chromosomal Abnormalities
DNA Fragmentation

Genetic disease
Environmental exposures
Varicocele

Placental disfunction/Hereditary trhombophilia
Infections
Uterine Malformations
Cervical incompetence



Ovulation **Fertilization** **Implantation** **Fetal Viability** **Healthy Liveborn**

POOR OOCYTE QUALITY
POOR OOCYTE MATURATION

Endometrial damage
Endometritis
Asherman sindrome

Maternal Age
Genetic disease
Lifestyle

Immunological factors:
APA sindrome/LES
celiac disease

Endocrinological disorders

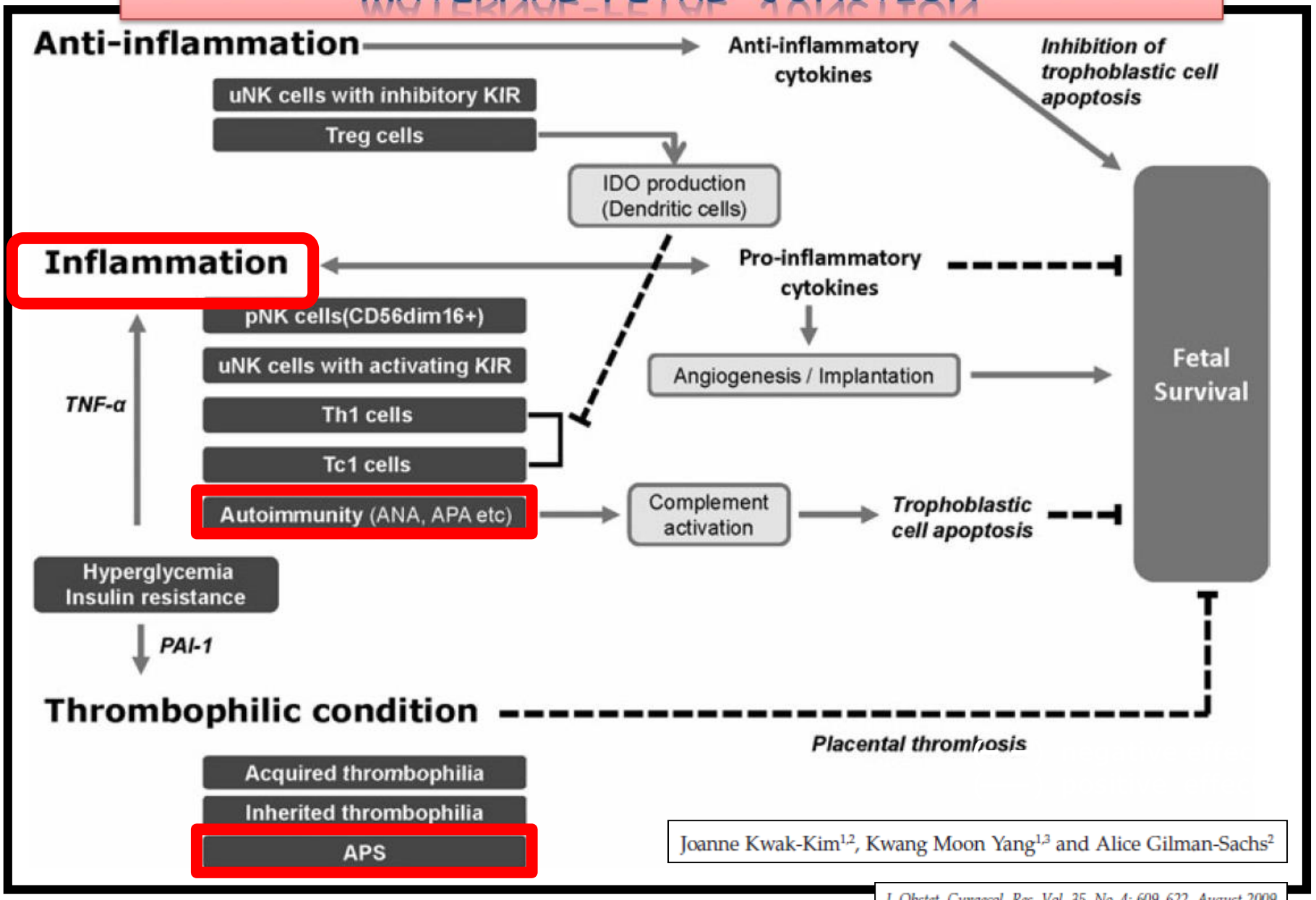
Luteal face insufficence/PRL disorders/Thyroid Disease
Insulin resistance (PCOS/Metabolic syndrome/Obesity)

Clinical and experimental research has clearly demostrated that a proper immunologic relationship betwen the mother and the conceptus is a key factor for successful pregnancy and strongly suggests that derangements in this immunologic dialogue can lead to serious complications of early gestation including RPL

However the specific factors involved in the developmet in a correct maternal-fetal immunologic interaction are still incompletely determined

Yoshinaga K, 2008; Kjersti M, 2006; Laird SM, 2003; Kwak-Kim J, 2009

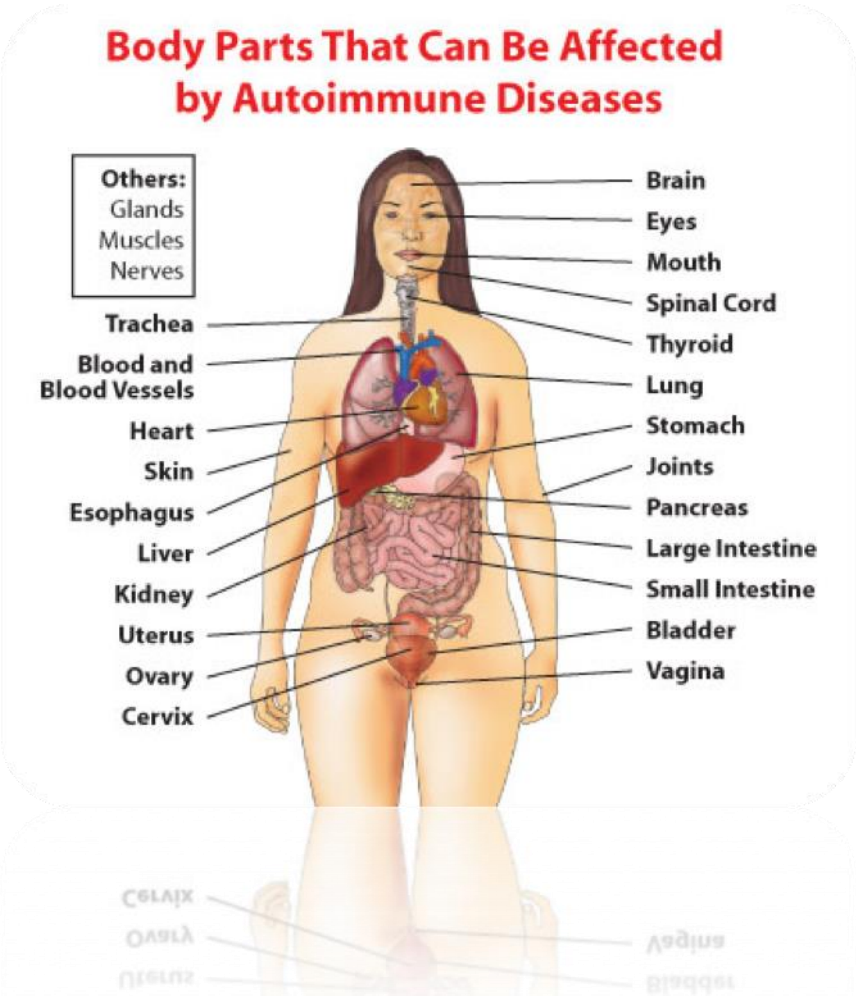
INFLAMMATORY-THROMBOTIC PROCESS AT MATERNAL-FETAL JUNCTION



Joanne Kwak-Kim[1,2], Kwang Moon Yang[1,3] and Alice Gilman-Sachs[2]

J. Obstet. Gynaecol. Res. Vol. 35, No. 4: 609–622, August 2009

AUTOIMMUNITY AND PREGNANCY

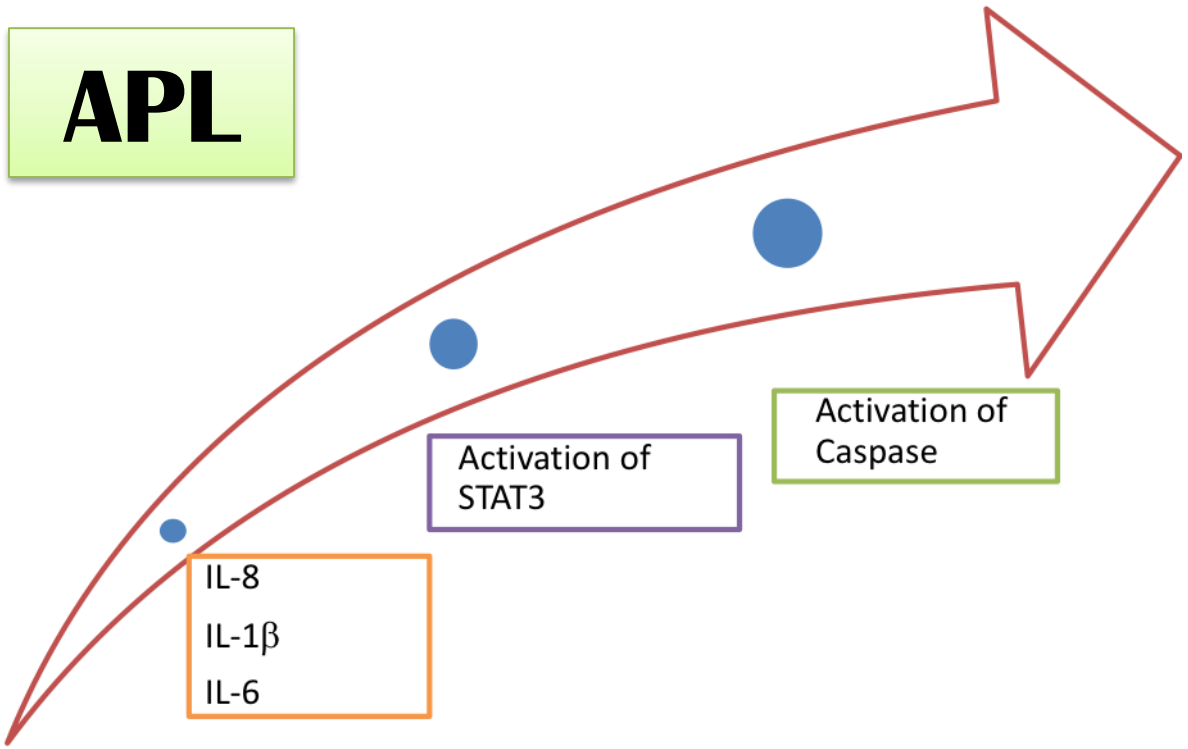


- Antiphospholipid Antibody Syndrome
- Autoimmune hepatitis
- Celiac disease
- Connective tissue diseases
- Autoimmune Diabetes
- Graves disease
- Guillaime Barré
- Idiopatic thrombocytopenia
- Inflammatory bowel disease
- Multiple sclerosis
- Myasthenia gravis
- Psoriasis
- Rheumatoid arthritis
- Sclerodermia
- SjÖgren syndrome
- Systemic Lupus Erythematosus (SLE)
- Autoimmune nephropaties

Management of Women with Recurrent Pregnancy Losses and Antiphospholipid Antibody Syndrome

Joanne Kwak-Kim[1,2], Maria Socorro L. Agcaoili[1,3], Lara Aleta[1,4], Aihua Liao[1,5], Kuniaki Ota[1,2], Svetlana Dambaeva[2], Kenneth Beaman[2], Joon Woo Kim[6], Alice Gilman-Sachs[2]

Am J Reprod Immunol 2013



THROPHOBLAST APOPTOSIS

IMPAIRMENT OF MIGRATION AND INVASIVENESS

- ✓ ***aPL has been shown to have a direct effect on throphoblast unrelated to thrombosis***
- ✓ ***aPL may induce direct cellular injury, apoptosis, inhibition of proliferation***
- ✓ ***Decreases HCG production***
- ✓ ***Induces defective invasiveness in the throphoblast***

AUTOIMMUNE DISEASE AND PLACENTAL COMPLICATION

SLE

SLE WITH ACTIVE DISEASE aPL RENAL DISEASE/HYPERT.

PREGNANCY WITH SLE

NORMAL PREGNANCY

Severe inflammatory dysfunction

Increasing systemic Inflammatory stress

Systemic Inflammatory stress

Inflammation

Complement activation

Direct throphoblast injury

Endotelial dysfunction

Acute atherosis

Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms

Human Reproduction Update, 2014

Chiara Tersigni[1], Roberta Castellani[1], Chiara de Waure[2],

- **OR for CD = 5.82 (95% CI 2.30-14.74) in RPL**
- **RR of miscarriage in CD = 1.39 (95% CI 1.15-1.67)**
- **The risk is significantly reduced by a gluten-free diet.**
- **Potential negative effects of active CD also in terms of reproductive performances, and of the importance of a strict diet to ameliorate their health condition and reproductive health.**

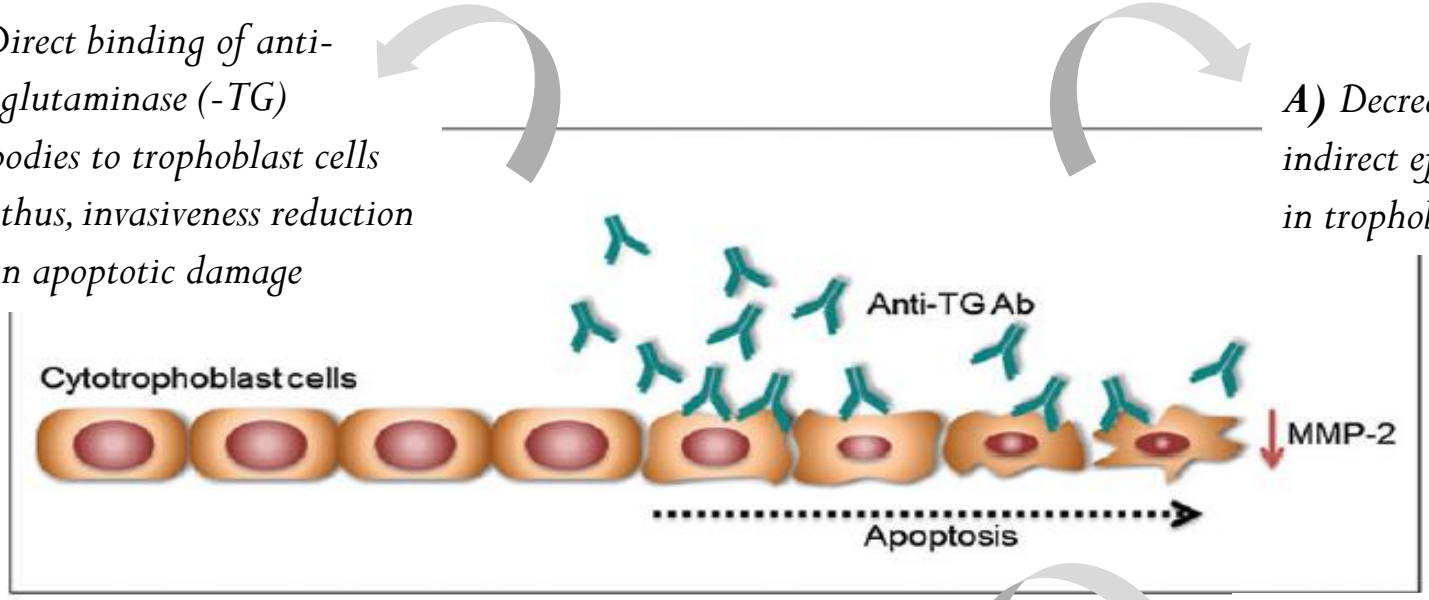
Physicians should investigate women with unexplained infertility, recurrent miscarriage or IUGR for undiagnosed CD
(only 20–50% of affected individuals have subjective symptoms!)

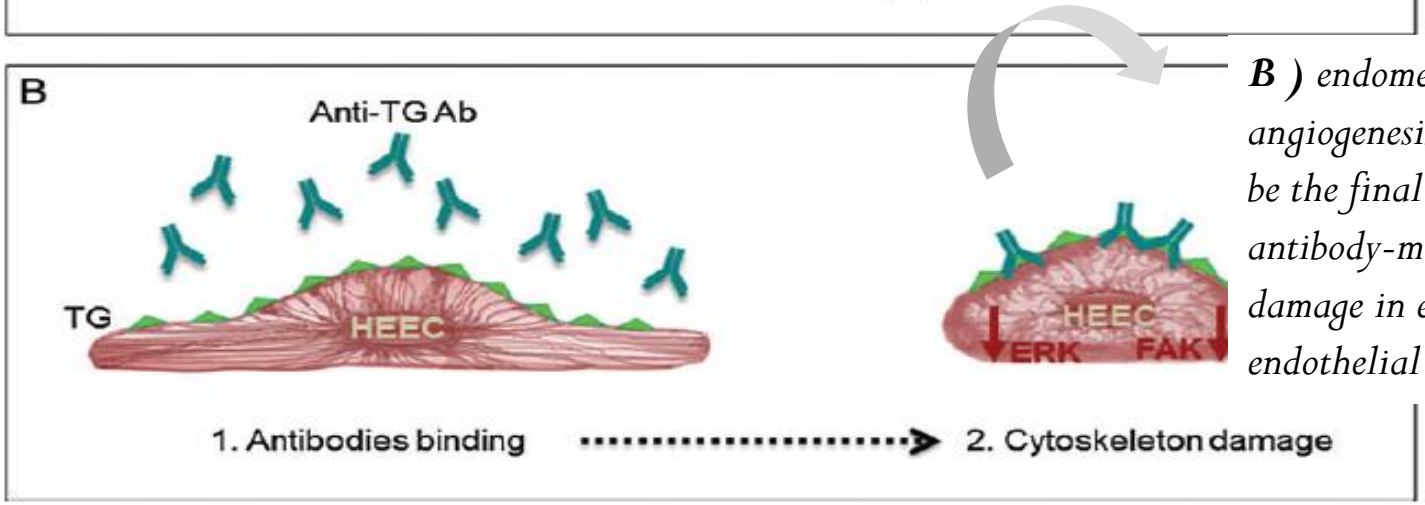
CELIAC DISEASE AND RPL: NOT ONLY MALABSORPTION…

anti-TG antibody-mediated implantation and placental damage

A) *Direct binding of anti-transglutaminase (-TG) antibodies to trophoblast cells and, thus, invasiveness reduction via an apoptotic damage*

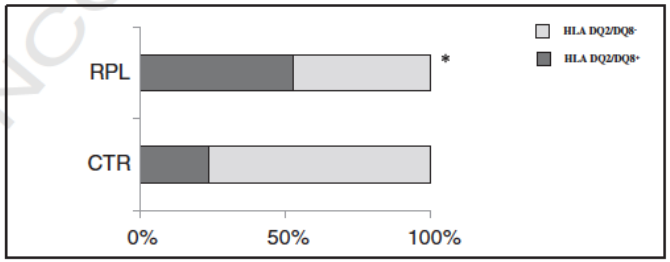
A) *Decrease in MMPs activity, indirect effect of the increase in trophoblast apoptosis*





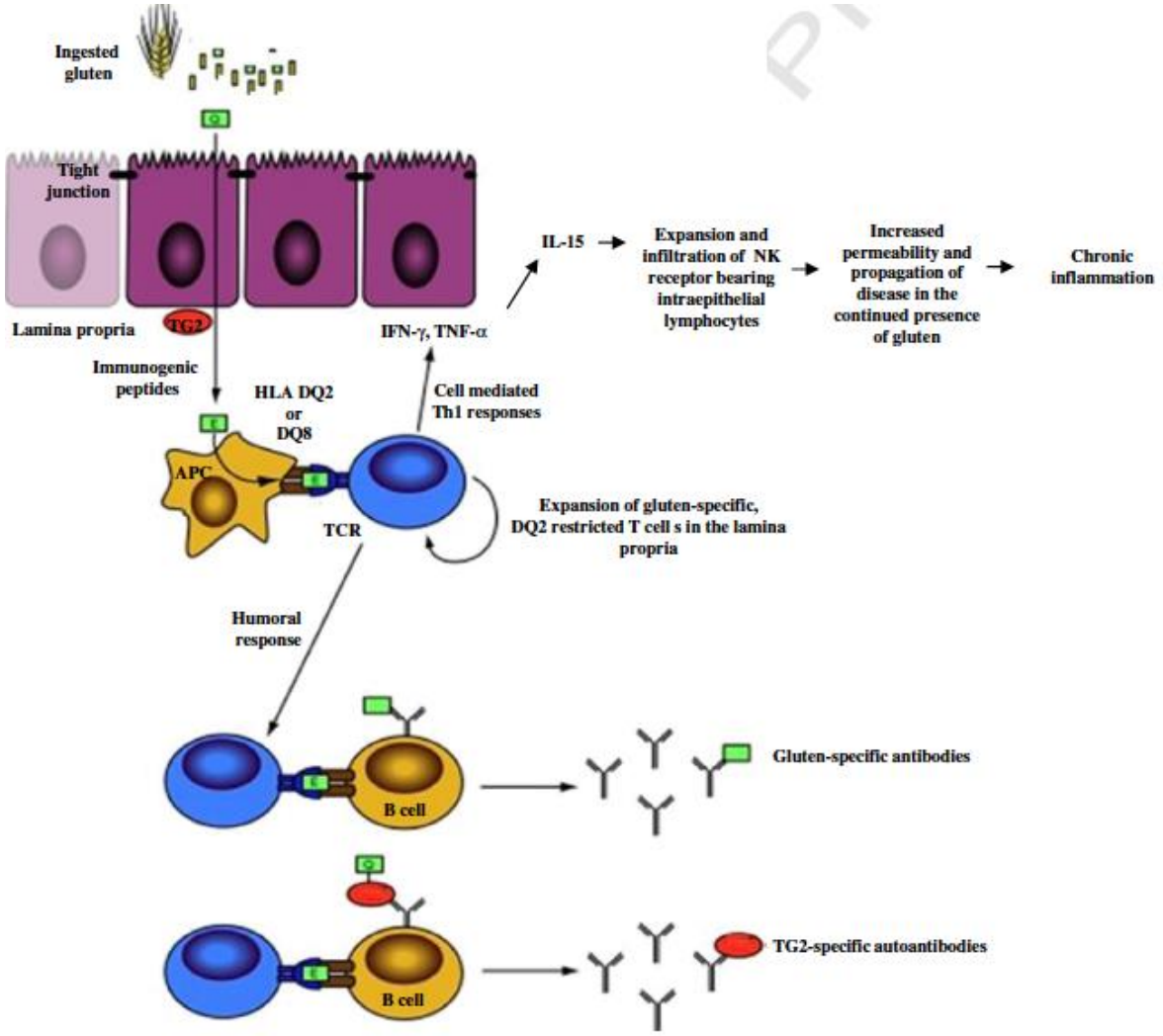
B) *endometrial angiogenesis. The angiogenesis inhibition seems to be the final effect of anti-TG antibody-mediated cytoskeletal damage in endometrial endothelial cells.*

Human leukocyte antigen (HLA) DQ2/DQ8 prevalence in recurrent pregnancy loss women



Prevalence of HLA-DQ2/DQ8 positivity in Recurrent Pregnancy Loss (RPL) and control (CTR) women.
*Statistical significance: p<0.05.

	CTR (n=55)	RPL (n=97)	P value
HLA DQ2/DQ8+ n (%)	13 (23.6%)	51 (52.6%)	<0.01



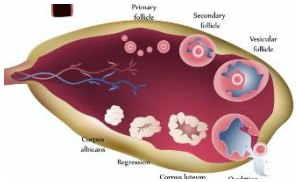
S. D'Ippolito et al. / Autoimmunity Reviews 2016

THE WAY TO ACHIEVE A HEALTHY LIVEBORN…

POOR SPERM QUALITY
Chromosomal Abnormalities
DNA Fragmentation

Genetic disease
Environmental exposures
Varicocele

Placental disfunction/Hereditary trhombophilia
Infections
Uterine Malformations
Cervical incompetence



Ovulation **Fertilization** **Implantation** **Fetal Viability** **Healthy Liveborn**

POOR OOCYTE QUALITY
POOR OOCYTE MATURATION

Endometrial damage
Endometritis

Asherman sindrome

Maternal Age
Genetic disease
Lifestyle

Immunological factors:
APA sindrome/LES
celiac disease

Endocrinological disorders

Luteal face insufficence/PRL disorders/Thyroid Disease
Insulin resistance (PCOS/Metabolic syndrome/Obesity)

Chronic endometritis and RPL

Chronic endometritis is a persistent inflammation of uterine endometrium.
Histologically, the diagnosis of chronic endometritis is based on the presence of plasma cells in the endometrial stroma.

Table 1 – Reported prevalence of chronic endometritis in various populations studied and the criteria used for diagnosis.

Authors	Prevalence of chronic endometritis, n (%)	Diagnostic criteria used
Recurrent pregnancy loss		
Zolghadri et al., 2011	61/142 (43.0)	H&E > one plasma cell/HPF
Cicinelli et al., 2014	190/360 (52.8)	H&E > one plasma cell/HPF
McQueen et al., 2014	35/395 (8.9)	H&E > one plasma cell in whole section
McQueen et al., 2015	60/107 (56.1)	>one CD138+ cells/HPF
Bouet et al., 2016	14/51 (27.5)	≥five CD138+ cells/10 HPF
Recurrent implantation failure		
Johnston-MacAnanny et al., 2010	10/33 (30.3)	>one CD138+ cells/HPF
Cicinelli et al., 2015	61/106 (57.5)	H&E > one plasma cell/HPF
Bouet et al., 2016	6/43 (14.0)	≥f ive CD138+ cells/10 HPF

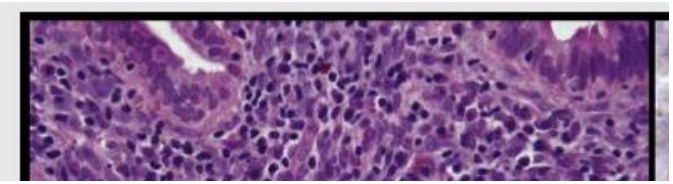
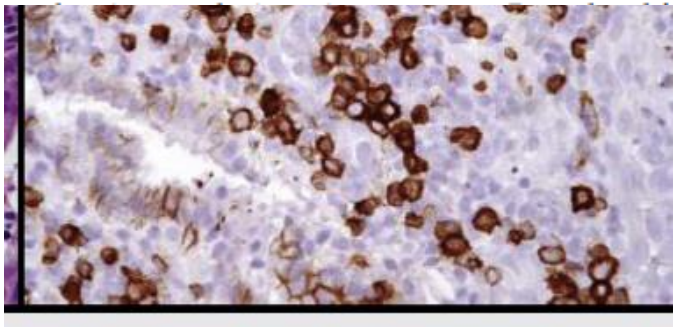


Table 2 Specific etiological agents of chronic endometritis in endometrial specimens of infertile women with repeated implantation failure

Corynebacterium	10/142 (7.0)
Enterococcus	15/142 (10.6)
Escherichia coli	14/142 (9.9)
Klebsiella pneumoniae	2/142 (1.4)
Streptococcus spp.	11/142 (7.7)
Staphylococcus spp.	12/142 (8.4)
Chlamydia trachomatis	2/142 (1.4)
Neisseria gonorrhoeae	0/142 (0)
Mycoplasma	12/46 (26.1)
Ureaplasma	20/46 (43.4)



REPRODUCTIVE BIOMEDICINE 2017

Chronic endometritis and RPL

360 women with unexplained RM

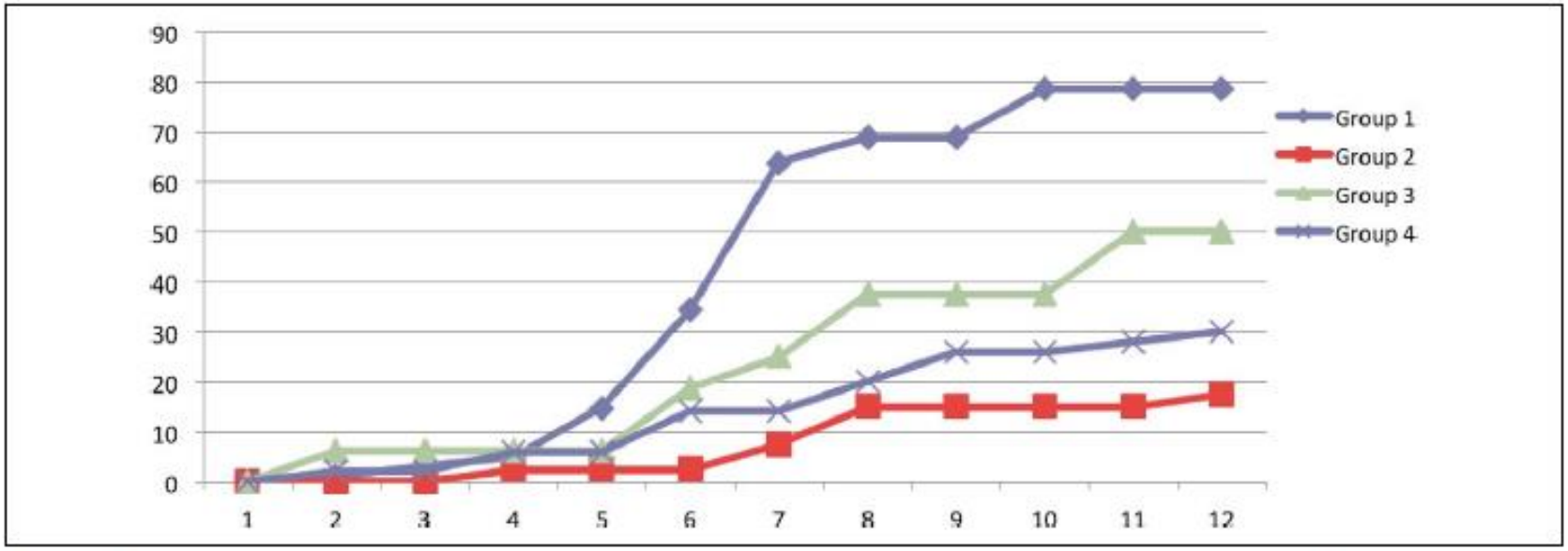


Figure 2. The percentage distribution of time, in months, in the beginning of the first successful pregnancy with live birth in the 4 groups of women with recurrent miscarriage and diagnosed with CE. CE indicates chronic endometritis.

1. antibiogram-based antibiotic treatment normalized hysteroscopy, histology, and cultures

2. CE was still present at hysteroscopy

3.positive at hysteroscopy, but not at cultures Hysteroscopy becomes normal after a CDC based therapy

4 CE was still present

Cicinelli E, Reproductive Sciences 2014,Vol. 21(5) 640-647

«the identification and treatment of CE has emerged as an important factor that should be evaluated when caring for women with RPL.»

THE HUMAN MICROBIOME PROJECT

CONTAINS **10** TIMES **MORE** MICROBIAL CELLS THAN HUMAN CELLS.

MICROORGANISMS, THEIR GENOMES & ENVIRONMENTAL INTER ACTIONS

250 HEALTHY PEOPLE

SPOTS SAMPLED:

PRI

DISMICROBISMO INTESTINALE ⇄ **DISMICROBISMO VAGINALE**

Alterata permeabilità parete intestinale

Infiammazione

ALTERATA OMEOSTASI APPARATO RIPRODUTTIVO

- **Infertilità**
- **Endometriti**

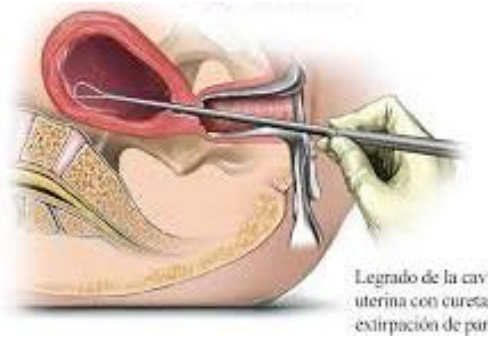
- **Abortività**
- Parto pretermine
- PROM
- Corioamniotiti
- Disfunzione placentare

- Dismetabolismo materno
- Obesità
- Patol autoimmuni

DANNO ENDOMETRIALE IATROGENO (Endometrite /S. Asherman)

RCU ripetuti

Terapia medica aborto??



What are the management options for early pregnancy loss?

Accepted treatment options for early pregnancy loss include expectant management, medical treatment, or surgical evacuation. In women without medical com- plications or symptoms requiring urgent surgical evacuation, treatment plans can safely accommodate patient treatment preferences.

PRACTICE BULLETIN

Early pregnancy loss

NOVEMBER 2018

Most women choose medical abortion because of a desire to avoid surgery, a perception that medical abortion is safer than surgical abortion, and a belief that medical abortion is more natural and private than a surgical procedure

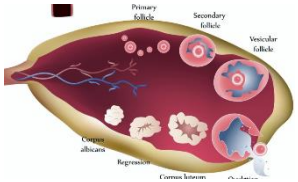
THE WAY TO ACHIEVE A HEALTHY LIVEBORN…

POOR SPERM QUALITY
Chromosomal Abnormalities
DNA Fragmentation

Genetic disease
Environmental exposures
Varicocele

Placental disfunction/Hereditary trhombophilia

Infections
Uterine Malformations
Cervical incompetence



Ovulation **Fertilization** **Implantation** **Fetal Viability** **Healthy Liveborn**

POOR OOCYTE QUALITY
POOR OOCYTE MATURATION

Maternal Age
Genetic disease
Lifestyle

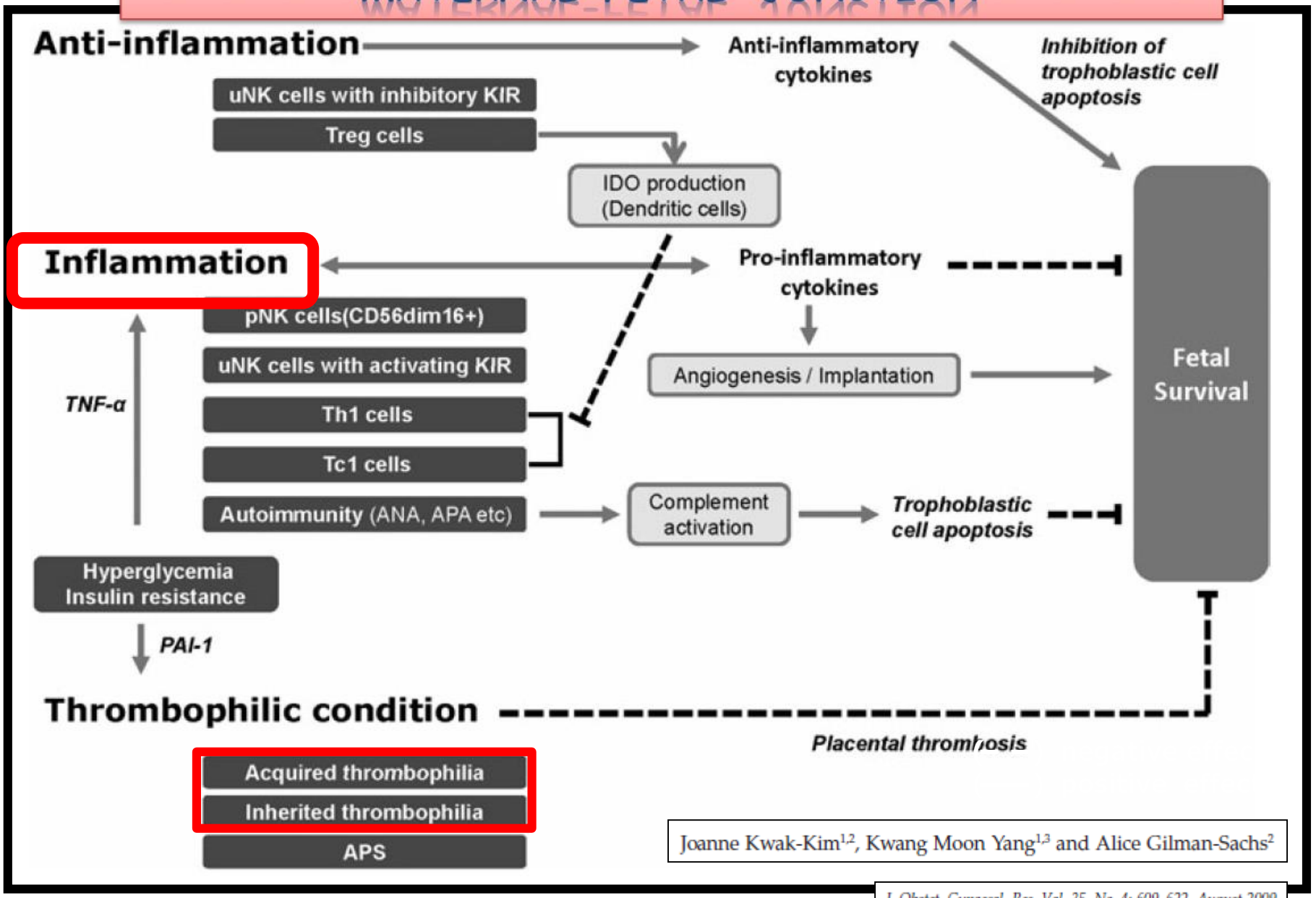
Endometrial damage
Endometritis
Asherman sindrome

Immunological factors:
APA sindrome/LES
celiac disease

Endocrinological disorders

Luteal face insufficence/PRL disorders/Thyroid Disease
Insulin resistance (PCOS/Metabolic syndrome/Obesity)

INFLAMMATORY-THROMBOTIC PROCESS AT MATERNAL-FETAL JUNCTION



Joanne Kwak-Kim[1,2], Kwang Moon Yang[1,3] and Alice Gilman-Sachs[2]

J. Obstet. Gynaecol. Res. Vol. 35, No. 4: 609–622, August 2009

ABORTO RICORRENTE E TROMBOFILIA

Available data suggest that both acquired and inherited thrombophilia are associated with an increased risk of early (recurrent) fetal loss.

Bates et al. Chest 2008

Table 6—*Risk of Early Loss in Women With Thrombophilia (Section 9.1)**

Type of Thrombophilia	Thrombophilia	No Thrombophilia	OR (95% CI)
Factor V Leiden (homozygous)	37/76	484/1,010	2.71 (1.32–5.58)
Factor V Leiden (heterozygous)	172/243	1,632/2,689	1.68 (1.09–2.58)
Prothrombin gene mutation (heterozygous)	53/75	657/1,356	2.49 (1.24–5.00)
MTHFR C677T (homozygous)	53/75	534/907	1.40 (0.77–2.55)
Antithrombin deficiency	2/8	54/196	0.88 (0.17–4.48)
Protein C deficiency	2/3	34/73	2.29 (0.20–26.43)
Protein S deficiency	3/4	33/72	3.55 (0.35–35.72)
Anticardiolipin antibodies	127/149	869/1,956	3.40 (1.33–8.68)
Lupus anticoagulantsb (nonspecific inhibitor)	59/107	581/1,728	2.97 (1.03–9.76)
Hyperhomocysteinemia	33/37	128/235	6.25 (1.37–28.42)

*Data are presented as No./total. Data derived from Robertson et al.[128]

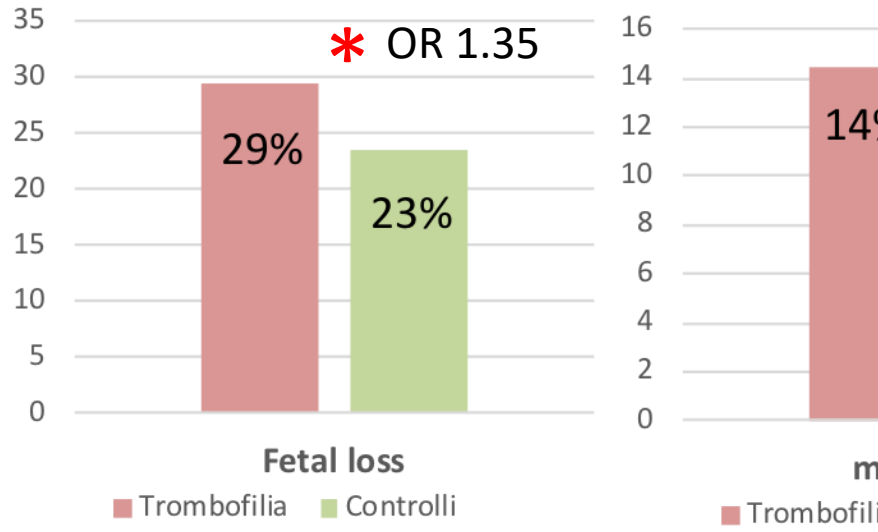
234 studi, principalmente retrospettivi

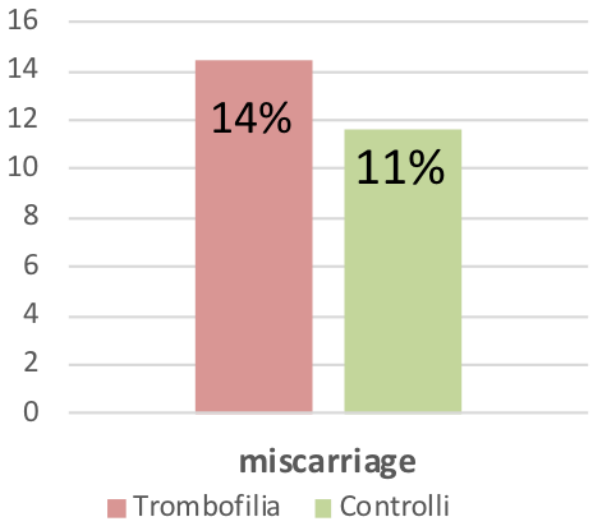
Robertson L. Br J Haematol 2005

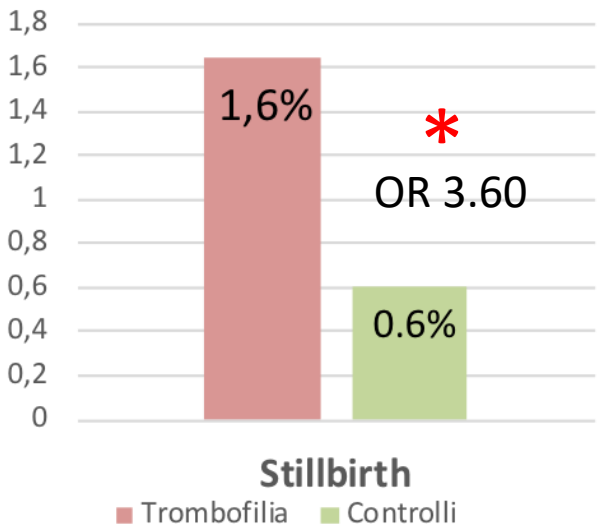
HEREDITARY TRHOMBOPHILIA AND FETAL LOSS

EPCOT STUDY

STRONG ASSOCIATION BETWEEN TRHOMBOPHILIA AND LATE , RATHER THAN EARLY, FETAL LOSS







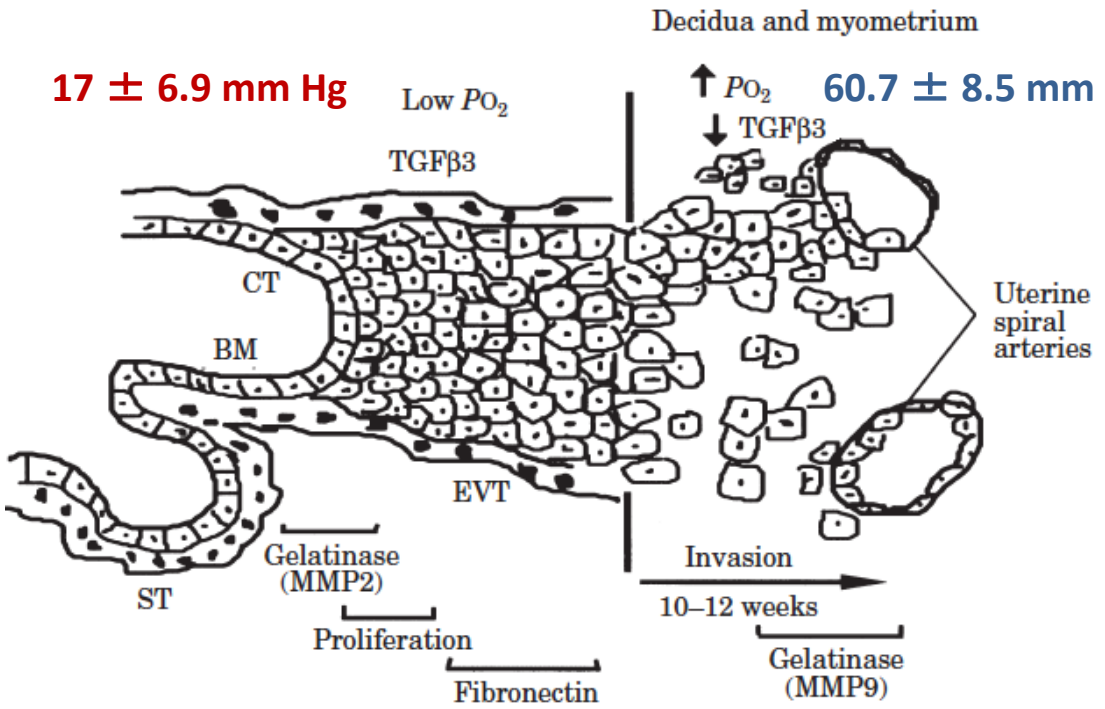
1524 gravidanze

Type	All spontaneous fetal losses	Miscarriage	Stillbirth
Antithrombin deficiency	2·1 (1·2–3·6)	1·7 (1·0–2·8)	5·2 (1·5–18·1)
Protein-C deficiency	1·4 (0·9–2·2)	1·4 (0·9–2·2)	2·3 (0·6–8·3)
Protein-S deficiency	1·3 (0·8–2·1)	1·2 (0·7–1·9)	3·3 (1·0–11·3)
Factor V Leiden	1·0 (0·6–1·7)	0·9 (0·5–1·5)	2·0 (0·5–7·7)
Combined defects	2·0 (0·5–8·1)	0·8 (0·2–3·6)	14·3 (2·4–86·0)

Lancet 1996; **348:** 913–16

HEREDITARY TRHOMBOPHILIA AND FETAL LOSS

STRONG ASSOCIATION BETWEEN TRHOMBOPHILIA AND LATE , RATHER THAN EARLY, FETAL LOSS



In early pregnancy placenta develops in relatively hypoxic conditions due to limited blood flow in the intervillous space. Intervillous blood flow increases around 10–12 weeks of gestation and results in exposure of trophoblast to increased oxygen tension.

CHORIONIC VILLOUS ORGANIZATION AT THE FETAL-MATERNAL INTERFACE IN THE FIRST TRIMESTER OF PREGNANCY

Thromb Haemost. 2004 Feb;91(2):290-5.

Maternal thrombophilias are not associated with early pregnancy loss.

Roqué H1, Paidas MJ, Funai EF, Kuczynski E, Lockwood CJ.

HEREDITARY TRHOMBOPHILIA AND RPL

For women with RPL, we suggest not to screen for hereditary thrombophilia unless in the context of research, or in women with additional risk factors for thrombophilia.	Conditional ⊕⊕⊕◯

	Association	Contributing factor	Prognosis	Treatment
Hereditary thrombophilia*	No/weak	Unclear	Yes	No

** this includes Factor V Leiden mutation - Prothrombin mutation - MTHFR mutation - Protein C, Protein S and Antithrombin deficiency*

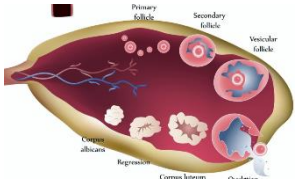
Trombofilia	Grado di associazione con RPL	trattamento
Mutazione fattore V Leiden	Possibile, ma >10 settimana	LMWH?
Mutazione fattore II	Bassa evidenza	LMWH?
Deficit proteina C, S, AT III	Nessuna evidenza	LMWH?
Mutazione MTHFR	Nessuna evidenza- RIFIUTATO!	
Iperomocisteinemia	Bassa evidenza	Stile di vita, folati, B6

THE WAY TO ACHIEVE A HEALTHY LIVEBORN…

POOR SPERM QUALITY
Chromosomal Abnormalities
DNA Fragmentation

Genetic disease
Environmental exposures
Varicocele

Placental disfunction/Hereditary trhombophilia
Infections
Uterine Malformations
Cervical incompetence



Ovulation **Fertilization** **Implantation** **Fetal Viability** **Healthy Liveborn**

POOR OOCYTE QUALITY
POOR OOCYTE MATURATION

Maternal Age
Genetic disease
Lifestyle

Endometrial damage
Endometritis
Asherman sindrome

Immunological factors:
APA sindrome/LES
celiac disease

Endocrinological disorders

Luteal face insufficence/PRL disorders/Thyroid Disease
Insulin resistance (PCOS/Metabolic syndrome/Obesity)

MALFORMAZIONI UTERINE

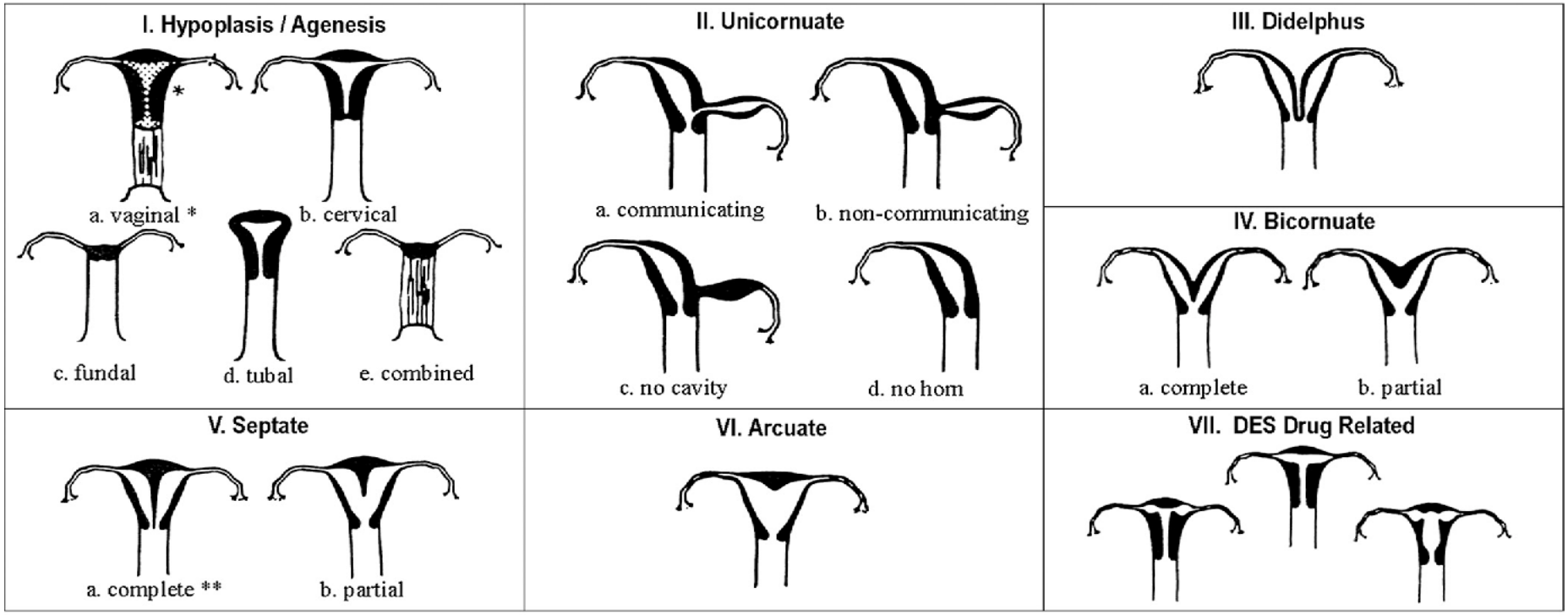


Table 2
Prevalence of congenital uterine anomalies in women with RPL and women in the general population

Anomaly	Prevalence in Patients with RPL (%)	Prevalence in the General Population (%)[6,7]
Bicornuate	1.2[a]	0.3–0.4

0,1% delle donne.

15-30% in RPL del II trimestre

the prevalence of uterine malformations appears to be **higher in women with second-trimester miscarriages** compared with women who suffer first- trimester miscarriages, but this may be related to the cervical weakness that is frequently associated with uterine malformation

Jaslow CR, Obstetrics and gynecology clinics of North America 2014

MALFORMAZIONI UTERINE

La terapia chirurgica (**Resezione isteroscopica)** viene attuata in caso di utero setto o sub-setto associato ad RSA

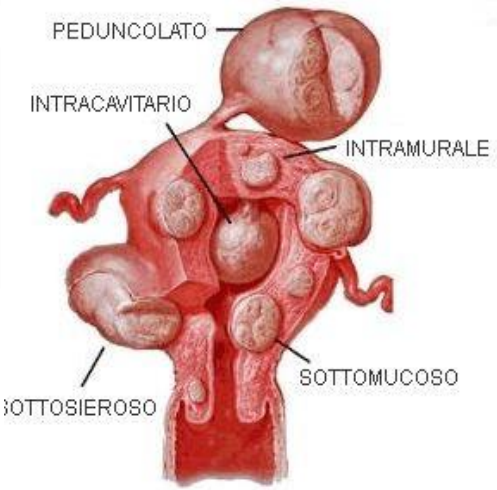
Whether hysteroscopic septum resection has beneficial effects (improving live birth rates, and decreasing miscarriage rates, without doing harm), should be evaluated in the context of surgical trials in women with RPL and septate uterus.	Conditional	⊕◯◯◯
Metroplasty is not recommended for bicorporeal uterus with normal cervix (former AFS bicornuate uterus) and RPL.	Strong	⊕◯◯◯

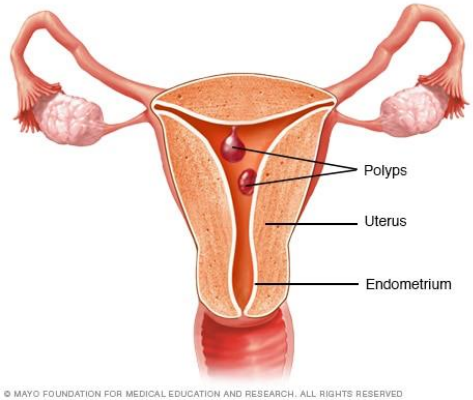
eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

ANOMALIE STRUTTURALI UTERINE ACQUISITE

There is insufficient evidence supporting hysteroscopic removal of submucosal fibroids or endometrial polyps in women with RPL.	Conditional	⊕◯◯◯
Surgical removal of intramural fibroids is not recommended in women with RPL. There is insufficient evidence to recommend removing fibroids that distort the uterine cavity.	Conditional	⊕◯◯◯
There is insufficient evidence of benefit for surgical removal of intrauterine adhesions for pregnancy outcome. After hysteroscopic removal of intrauterine adhesions in women with RPL, precautions have to be taken to prevent recurrence of adhesions.	Conditional	⊕◯◯◯

Sintomatologia



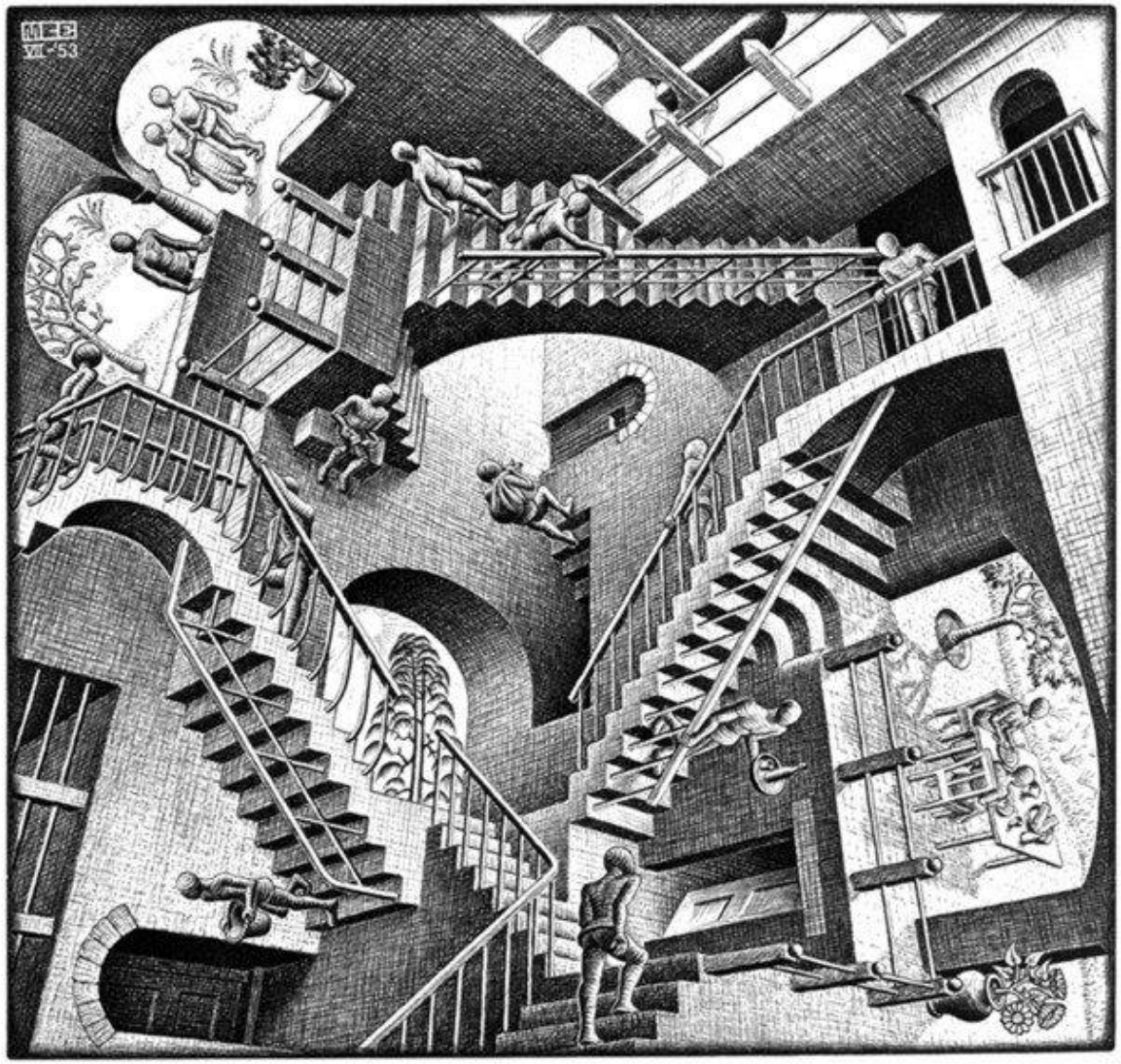


RECURRENT PREGNANCY LOSS

Recurrent miscarriage is an heterogeneous condition that has many possible causes.

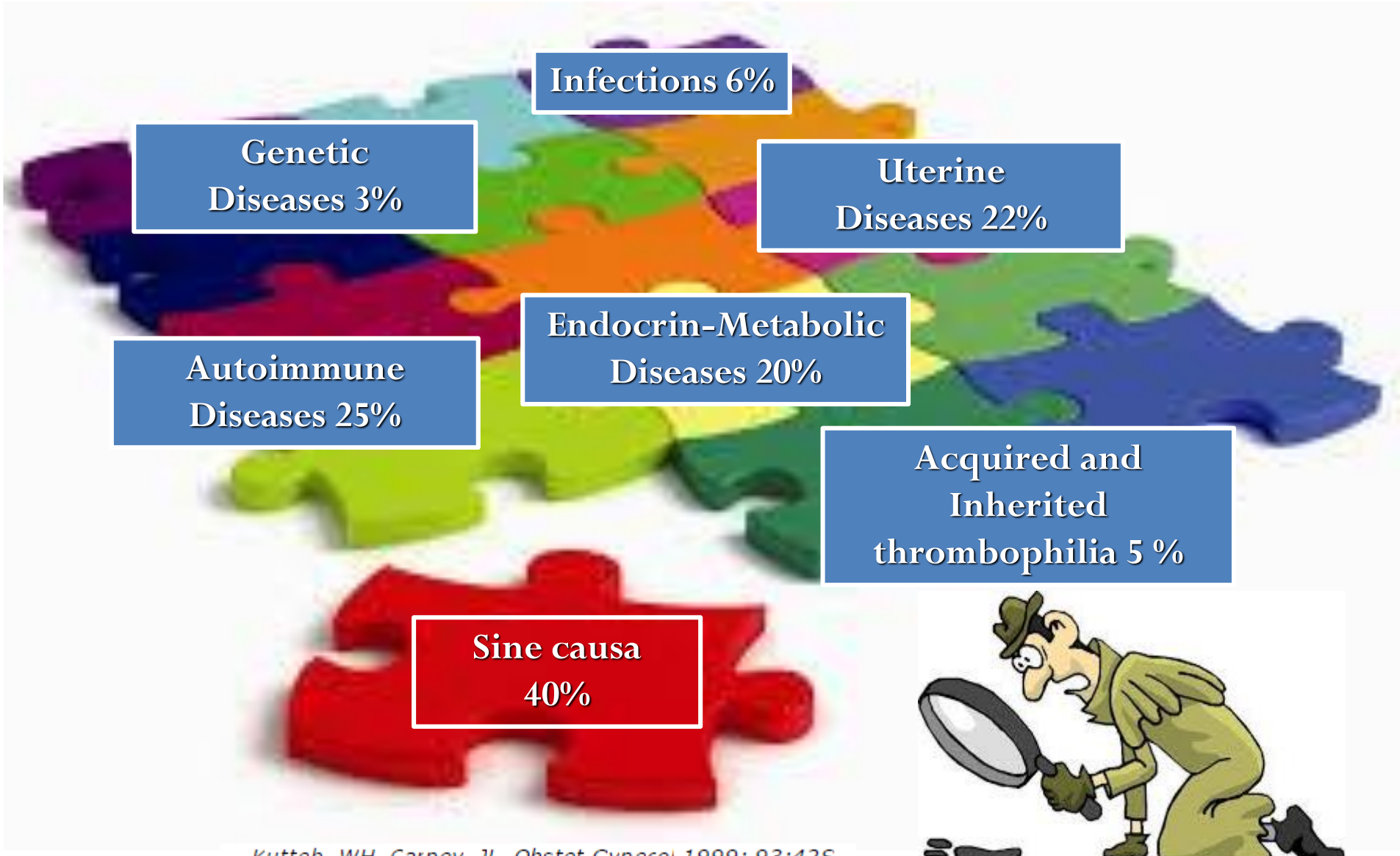
More than one contributory factor may underlie the recurrent pregnancy losses.

Royal College of Obstetricians and Gynaecologist, 2003



Che Fare?

CONSIDER MULTIPLE AETIOLOGYS



Kutteh, WH, Carney, JL. Obstet Gynecol 1999; 93:42S.

UNEXPLAINED RECURRENT PREGNANCY LOSS

Clinical diagnosis of «**unexplained RPL**» is made when other possible evaluation options are exhausted

However

The repertoire of clinical evaluation and assay varies significantly based on local availability and the physician's knowledge

Therefore

Women with «unexplained» RPL should be considered heterogeneous with regard to cause and treatment

..ricominciamo da un'attenta **ANAMNESI**

- **A. FAMILIARE:**

- anomalie congenite o genetiche
- patologie croniche (es. dismetabolismo glucidico)
- patologia trombo-embolica in età giovanile
- età della menopausa materna

- **A. FISIOLOGICA/PATOLOGICA/OSTETRICA**

- indice ponderale alla nascita
- stile di vita (farmaci, fumo, alcol, droghe)
-patologie croniche
-età d' inizio della attività sessuale e numero dei patners
- età menarca e caratteristiche cicli mestruali
- interventi chirurgici sull' utero
- meteorismo dopo l'assunzione di CHO
- sintomi di disendocrinie (galattorrea, distiroidismo…)
- precedenti ostetrici

..ricominciamo da un'attenta **ANAMNESI**

..e cosa indagare nel compagno?

- **A. FAMILIARE e PERSONALE:**

- anomalie congenite o del cariotipo
- patologie croniche
- patologia vasculo-trombotica in età giovanile.

- **A. FISIOLOGICA e PATOLOGICA:**

- meteorismo dopo l'assunzione di carboidrati
- stile di vita (fumo, alcol, droghe, farmaci)
- patologie croniche
- informazioni disponibili per precedenti indagini di laboratorio o strumentali

APPROCCIO ALLE COPPIE CON RPL

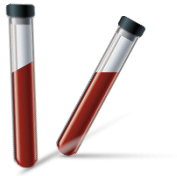
ESAME OBIETTIVO

- peso, altezza, BMI, BIA
- distribuzione prevalente del grasso corporeo
- pressione arteriosa
- segni di endocrinopatia: irsutismo, galattorrea, tiroide
- anomalie uterine, lacerazioni cervicali

INDAGINI LABORATORISTICHE DI SUPPORTO

- **ESAMI EMATICI:**

FSH, LH, PRL, 17 β-E2, AMH, inibina B, TSH, AC anti TPO, ACA, LAC, anti β2-GP1, mutazione Leiden gene V, mutazione gene II, PAI1, fibrinogeno, proteina C, proteina S, valutazione IR

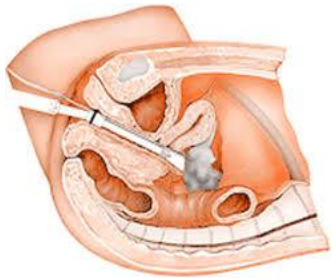


- **CARIOTIPO DELLA COPPIA**

INDAGINI STRUMENTALI DI SUPPORTO

- **ECOGRAFIA TRANSVAGINALE/TRANSADDOMINALE**

policistosi ovarica /anomalie uterine (setto, fibromi, adenomiomi,)



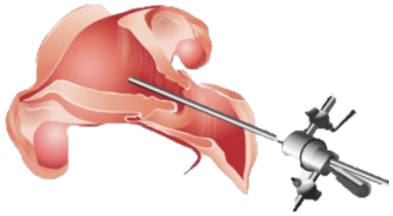
- **SONOISTERO/ISTEROSALPINGOGRAFIA**

anomalie uterine(setto, bicorne, incompetente),pervietà tubarica

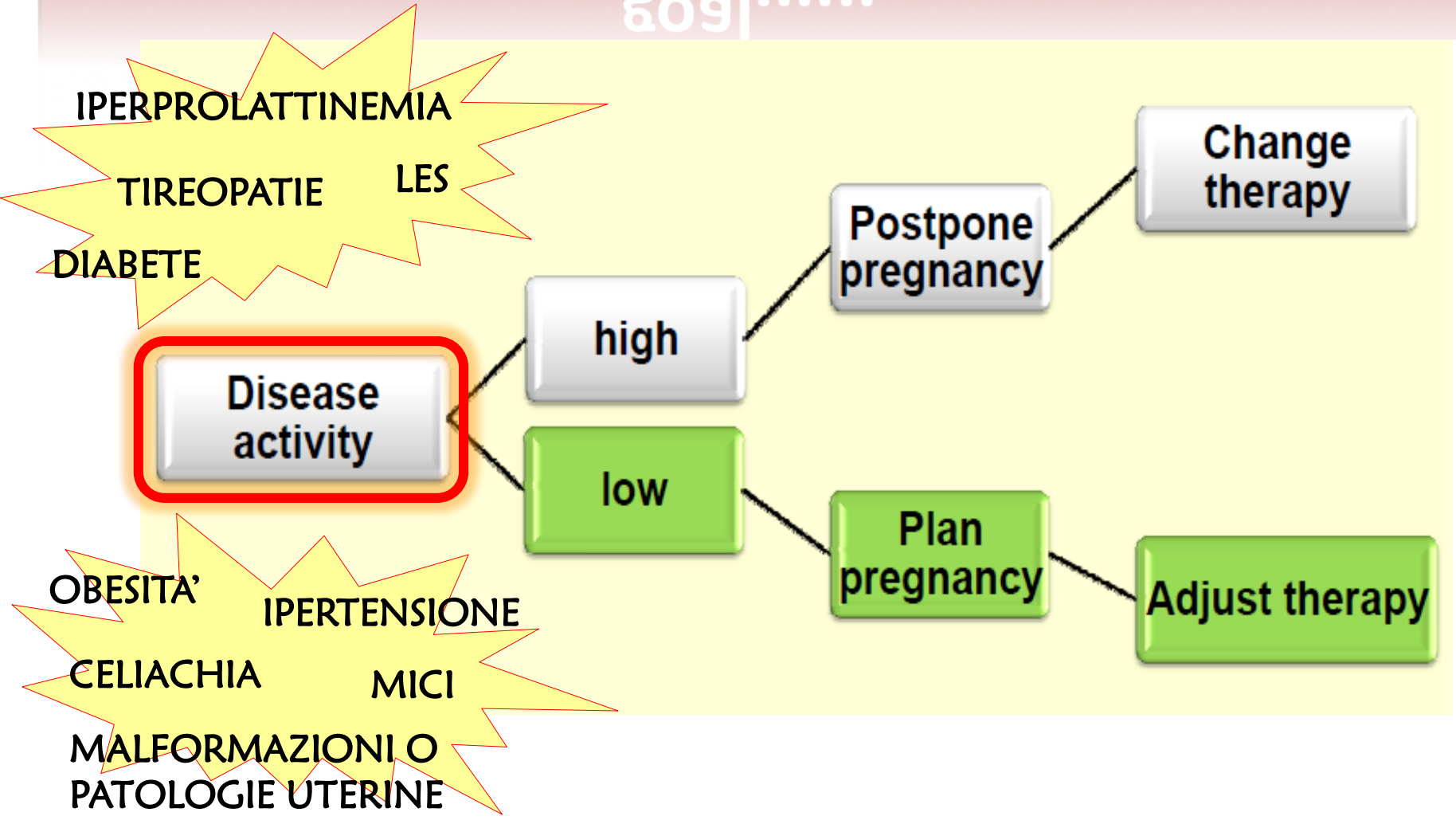
- **ISTEROSCOPIA**
- lesioni intrauterine

- **BIOPSIA ENDOMETRIALE**

endometrite cronica/ deficit della fase luteale



Inactive disease is a preconceptional goal……



PREGNANCY : A MILD INFLAMMATORY STATE

ADVERSE PREGNANCY OUTCOMES SEEM TO BE RELATED WITH AN EXAGGERATION OF THE NORM…

CORRECTION AND PREVENTION OF '*INFLAMMATORY / THROMBOTIC*' *PROCESS* CAN BE CONSIDERED AS THERAPEUTIC APPROACHES FOR INFERTILITY AND PREGNANCY LOSSES AS WELL AS LATE PREGNANCY COMPLICATIONS

Correzione abitudini di vita

PERDERE PESO IN ECCESSO

SEDENTARIETA'

ALIMENTAZIONE

FUMO, ALCOL, DROGHE

Take-home message

Education of both patients and profesional care takers

Preconceptional counseling to evaluate and avoid couple conditions that can interfere with RPL

Optimitation of ovoocites quality and maturation

Reproducing phisiological condition for conception and implantation

Optimitation of vaginal and gut microbiome

But first of all pay attention to listen
and remember that

The Couples with pregnancy loss need
Explanations, Frankness, Empathy and Understanding.


To obtain a "healthy newborn"
we have to start from the soil and the roots
caring for it, day by day, like a tree
GRAZIE PER L'ATTENZIONE