RECURRENT ABORTION:

FROM Pathophysiology
TO THE CLINICAL DIAGNOSIS

Claudio Giorlandino

THE SOUL OF A MAN MUST TRY SEVERAL TIMES TO ENTER THE MOTHER'S WOUMB BEFORE BEING BORN.

ONLY IN THIS WAY HE CAN BE CALLED SON OF THE MUSES AND HE WILL LOVE SCIENCE AND BEAUTY

PLATO "Fedro"

In the years since 1960 all abortions were **infectious and / or metabolic** tuberculosis, Leisteriosis and diabetes were sought.
Antibiotic therapies were prescribed.
There was considerable positive feedback.

For a few years the "preventive cerclage"
were made ...
with great success!

The doctors got certainty to get the solution!

Since the late 60s and almost all the '70s all abortions were considered **hormonal**.

Progesterone an combined Oestrogens were prescribed.

The doctors boasted successes.
Continue successes!

The doctors got certainty to get the solution!

In the '70s /' 80s all was **autoimmunity**: APS in particular.

It was prescribed aspirin but, the most "modern", began with cortisone.

The cases were exciting.

The doctors gathered affirmations, popularity, fame!

The doctors got certainty to get the solution!

In the late '80s and for most of the' 90s, the most "bizarre" therapies for APS such as **immunoprophylaxis** was sperimented with the “G-Immunoglobulines sensibilization”

They boasted amazing results.

Patients list themselves for these expensive (useless) treatments.

The doctors got certainty to get the solution!

At the end of the millennium **thrombophilia** triumphed.
Another "novelty".

It began with the Heparin and the Aspirin came back into vogue.

The doctors expert in abortion's therapy devoted themselves to this boasting continuous successes.

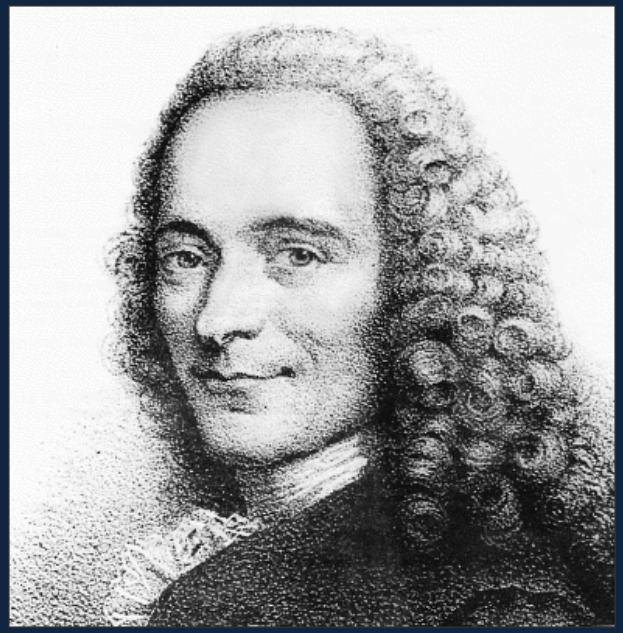
The doctors got certainty to get the solution … .

At the first decade of new millennium several conditions were considered causative
Such Thiroiditis, celiachia, PCO and more …..
Another "novelty".

Tiroxin began one of the most used therapy

The doctors expert in abortion's therapy devoted themselves to this boasting continuous successes.

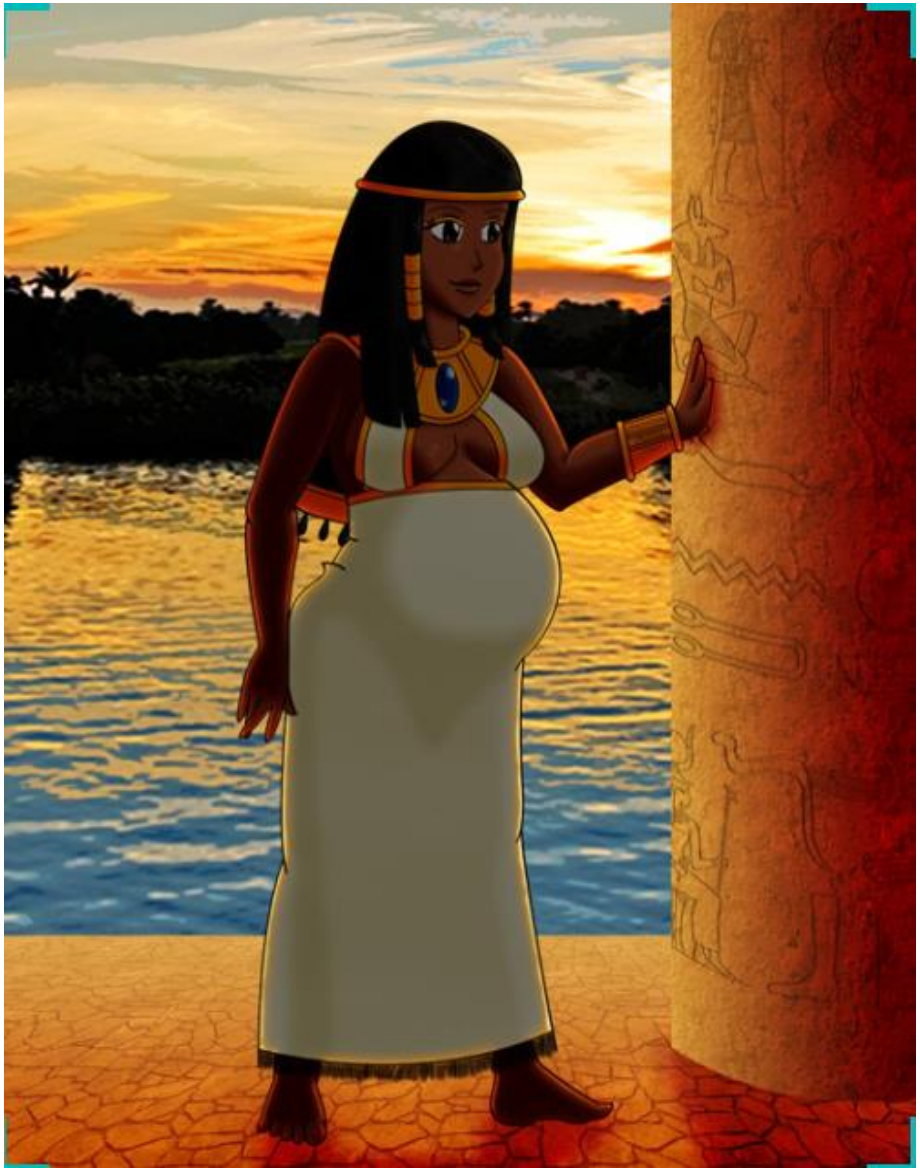
The doctors got certainty to get new solution … .



"Doubt is not a pleasant condition, but certainty is ridicolous.
Only idiots are sure of what they say "

Voltaire

Let’s GO BACK in THE TIMES….



We reflect.
if hundreds of generations believed that drinking the water of the Nile ,with the dust of the temple of Phile, preserves pregnancies, it means that even the sandstone of the temple worked … or not!

May be this worked as it looked like they worked our therapies in the past decades!

What is not working?
First of all, the differential diagnosis between:

- **spontaneous sporadic pregnancy loss**
- **recurrent pregnancy loss**

Too many occasional spontaneous abortions are considered (and consequently treated) as recurrent abortions!

The remarkable inefficiency of human reproduction is largely the result of spontaneous fetal aneuploidy.

Overall, 50%–70% of specimens from sporadic spontaneous losses show some type of cytogenetic abnormality,. Other 30% presents subchromosomal aberration

The most common karyotypic defects being autosomal trisomies (60%), monosomy X (20%), and polyploidy (20%) [1] Typically, numerical aneuploidy results from random germ cell meiotic nondisjunction in the germ cells of couples with normal parental karyotypes

Approximately 30% of spontaneous miscarriages are associated with subchromosomal abnormalities. Identification of these sub karyotypic abnormalities from chromosomal microarray analysis (CMA) helps to estimate recurrence risks in future pregnancies [1 2 3 4]

1- Silver and Branch 2007
2- Dhillon RK, et al. BJOG. 2014
3- Shah MS, et al. Fertil Steril. 2017.
4- Lathi RB, et al. PLoS One. 2012.

Supporting the concept that many losses among *Spontaneous Sporadic Pregnancy Loss* (SSPL) patients are the result of random, nonrecurring events is the fact that the prognosis for subsequent pregnancies in SSPL couples is better after an aneuploid miscarriage than after an euploid miscarriage. [1] [2]

Euploid miscarrage are more frequent among *Recurrent Pregnancy Loss* (RPL) couple. [3] [4] [5]

1- Warren and Silver 2008
2- Suzumori and Sugiura-Ogasawara 2010
3- Warburton et al. 1987
4- Ogasawara et al. 2000
5- Carp et al. 2001.


Did you aborted?
In any case:
Test! Test! Test!
Therapy ! Therapy!
Therapy!

Risponde dal 2017 il **medico** **Drxxxxx** Esercita a: xxx

Gentile utente, Le inivio gli esami che sono solito prescrivere nei casi come il Suo.

- Anticorpi anti: Nucleo – DNA – Fosfolipidi totali - Cardiolipina (ACA IgM ed IgG) – Endotelio – Muscolo liscio - Antigene microsomiale tiroideo – Tireoglobulina – ENA – Beta 2 Glicoproteina IgM ed IgG – Endomisio – Gliadina - Transglutaminasi
- Dosaggio frazioni C3 e C4 del complemento
- Dosaggio Immunoglobuline sieriche totali e frazionate
- Dosaggio glicemia a digiuno, Insulinemia ed Hb Glicosilata
- Dosaggio Uricemia, GOT, GPT, LDH, Elettroliti
- Prelievo per QPE, Emocromo completo, Es. Urine con valutazione del sedimento urinario
- Tests e dosaggio degli Immunocomplessi circolanti
- Ricerca cellule LE
- Tests e ricerca del LAC (Lupus anticoagulant) e dei fenomeni LAC-correlati (KCT, RVVT) (se positivi, ripetere dopo 8 settimane)
- Tipizzazione linfocitaria e sottopopolazioni (CD3, CD4, CD5, CD8, CD19, CD20, CD15/56, CD23, CD25)
- aPTT, PT, Fibrinogeno, AT III, D-Dimero
- Tests per trombofilia congenita: Omocisteinemia a digiuno
- Dosaggio Proteina C attivata
- Dosaggio Proteina S attivata
- Valutazione della resistenza alla proteina C attivata
- Ricerca mutazione Leiden del Fattore V
- Ricerca della mutazione G20210A del fattore II
- Ricerca mutazione dell'enzima MTHFR e delle sue varianti all'eliche principali
- Tests per ipofibrinolisi congenita Polimorfismo PAI 1 (ricerca genotipo 4G/4G)
- Polimorfismo ACE (ricerca genotipo ACE D/D)
- Ricerca mutazioni fattore XIII
- Ricerca mutazioni fattore XII
- Dosaggio di Progesterone e PRL in 18° e 21° giorno del ciclo, contando dal primo giorno del flusso mestruale
- Tampone vaginale e cervicale per: germi comuni, Ureaplasma, Mycoplasma, Chlamydia
- Citologia endometriale (ricerca plasmacellule) su prelievo dedicato (per-isteroscopico, Vabra, Endocyte)
- Cariotipo della coppia su linfociti del sangue periferico
- Dosaggio fT3, fT4, TSH
- Isteroscopia

We have observed a trend whereby some fertility specialists (most of whom are reproductive endocrinologists) are referring difficult cases, especially those involving multiple miscarriages in patients with autoantibodies , to fertility immunologists.

At first glance, this appears commendable, but over the last few years, we have become aware of increasing instances in which vulnerable, anxious, and often desperate women are billed thousands of dollars for immunologic tests and HLA typing of questionable value, and are diagnosed as having "subclinical autoimmunity or thyroiditis" or Hereditary thrombophilia .

As a consequence, ***patients may be treated antenatally with Thiroxin, aspirin, heparin, prednisone or immunoglobulin maybe for a simple genetic polymorphism, even though they are asymptomatic.***

(Norbert Gleicher , 1999)

"Patients may be tested and are given heparin , aspirin and/or prednisone antenatally.

The treating physicians may then claim high reproductive success rates for these women.

However, many of these patients would have had successful pregnancies with no or minimal intervention.

*For example, in a study of 85 patients who had at least 3 spontaneous abortions without obvious cause, 86% of patients who were given prenatal "**tender loving care**" had a successful subsequent pregnancy.*

(Daniel J Wallace, 1996)

“the most widespread disease is the diagnosis”
So be careful not to make a diagnosis until you are sure there is illness!
Karl Krauss

Sigra «Maria Rossi». History of 5 abortions:

- First pregnancy:
Abortion at 6 weeks. hCG stops around 800, no embryo. Spontaneous bleeding.

- Second pregnancy: treated with ***progesterone***
14 weeks. Firm embryo at 42 mm. Chorionic villi Histology: plasma cells together with macrophages and lymphocytes

Third pregnancy: does ***progsteron and aspirin***: microaborto

Fourth pregnancy: immediately begins ***aspirin and Clexane 4,000***
Internal abortion at 9 weeks: histology for villi edema and dysmorphic

Fifth pregnancy: immediately start ***progesteron ,aspirin and Clexane 4000 x 2***:
Ended with a spontaneous abortion at 8 weeks ends with significant bleeding from thrombocytopenia. Villi not developed.

Sigra Maria Rossi.

This is Marco!
Sixth pregnancy (**none therapy**):
born at term (TC) 3,400 grams

How many?

Abortion

In Italy there are at least 60,000 spontaneous pregnancy interruptions each year.

In 2015 there were 18.8% of all live births

36.7% occurred up to the 8th week of amenorrhea

32.4% occurred between the 9th and 10th week.

17.2% occurred between the 11th and 12th week.

5.4% occurred between the 13th and the 15th week.

3.9% occurred between the 16th and the 20th week.

1.7% occurred between the 21st and the 25th week.

the remaining 2.7% in an unspecified period.

Recurrent abortion 1% of fertile women (maybe 600? … not more!)

It is not always a case.

In fact, if we calculate that the risk of losing a pregnancy ranges from 10 to 15%, if you perform a statistical calculation the possibility that if they have 3 consecutive, pour chance, it is only 0.34%.

When?

Ultrasound Findings	Gestational Age from LMP (days)	Approximate HCG (IU)	Approximate Risk of Miscarraige
Gestational sac	23–29	1500	<12%
Yolk sac	32–45	5000	<9% [†]
Embryonic disk	35–45		<8%
Fetal cardiac activity	42 with CRL > 5 mm	13000–15000	<8%
Embryo 2 cm with heart rate	56		<2%

CRL, crown–rump length; HCG, human chorionic gonadotropin; LMP, last menstrual period.

pathogenesis?

CLINICAL ABORTION UNITARY THEORY OF VASCULAR PATHOGENESIS

(or of the Younis thrombosis)

- **VERY EARLY** (anembrionic) generally recognize an **arterial vascular pathogenesis**: relative to the implantation site:
  - relative to the mother: uterine malformation
  - relative to the embryo: genetics
- **PRECOCIUS** (embryonic) generally recognize an **arterio-venous vascular pathogenesis:**
  - genetic imbalancement/infectious / inflammatory
- **TARDIVES** generally recognize a **venous vascular pathogenesis**.
  - genetic imbalancement . autoimmune thrombosis

Etiology?

Biomarker/lifestyle factor in patients with miscarriage/recurrent miscarriage	Documentation for causality	Possible treatment and its documented effect	Future research
Parental chromosome abnormalities [4, 5]	Strong	PGD: weak	Identification of high risk carriers through clinical history; RCT of PGD/no PGD
Autoantibodies [6, 7]	Moderate	Prednisone, IvIg: weak	RCTs of prednisone and/or IvIg
NK cell dysfunction [8, 9, 10]	Weak to moderate	Prednisone, IvIg: weak	Develop standardized methods of measuring NK cells in the endometrium; establish normal values of NK cells in the blood and endometrium during pregnancy
Abnormal HLA-G expression [11]	Weak to moderate	Prednisone, IvIg: weak	Develop standardized methods for measuring soluble and membrane-bound HLA-G
Hereditary thrombophilia [12, 13]	Moderate	Heparin, LDA: weak	RCTs of heparin and LDA
Acquired thrombophilia [12, 14]	Strong	Heparin, LDA: moderate	Larger RCTs of heparin and LDA

Etiology?

Biomarker/lifestyle factor in patients with miscarriage/recurrent miscarriage	Documentation for causality	Possible treatment and its documented effect	Future research
Thyroid autoimmunity [15, 16, 17]	Weak to moderate	Levothyroxine: weak	RCTs of levothyroxin
PCOS [18]	Weak	Weight loss	Cohort studies of miscarriage rates subsequent to weight loss vs no weight loss
Sperm DNA fragmentation [19, 20]	Moderate	Sperm separation: no	Identify the most specific assays; establish methods for efficient sperm selection.
Disrupted endometrial selection [21, 22, 23, 24, 25, 26]	Recently proposed mechanism	Correction of decidual selective phenotype by hormonal modulators, including progesterone.	Intervention studies using hormonal treatments in the early luteal phase are being carried out
Uterine malformations [27, 28]	Strong	Septal resection	RCTs of septal resection/no resection
hCG gene polymorphisms [29, 30]	Weak to moderate	hCG supplementation: weak	RCTs of hCG supplementation
Alcohol consumption [31]	Moderate	Alcohol cessation	NA
Obesity [32, 33]	Weak to moderate	Weight loss: weak	Cohort studies of miscarriage rates subsequent to weight loss vs no weight loss

GENERAL PRINCIPLE

The two major causes of miscarriage are uterine malformations and chromosomal (genetic) abnormalities. The third APS

CAUSA	% DI INCIDENZA	RISCHIO DI RICORRENZA
Aborti genetici (cromosomici e genici)	> 85% (per lo più occasionali)	10-15% (check genitori)
Malformazioni uterine	Dall'1 al 5 % *	> 50% (utero setto)
Patologie autoimmunitarie	Dall'1 al 3 % *	Circa 50%
Infezioni in atto	Dal 1 al 5 % *	Occasionale
Gravi patologie materne in atto	Circa 1 % *	Rischio elevato
Traumi / avvelenamenti / radiazioni ecc	Riscontri occasionali	Contingente

Gabbe: Obstetrics, 6th ed. - 2013 - Churchill Livingstone, Elsevier
ESHRE: 2017

GENERAL PRINCIPLE

All the other maternal factors **increases the risk** of miscarriage including thyroiditis, PCO, internal leiomyomata and, very hardly ever, cervical incompetence.

CAUSA	RISCONTRI IN LETTERATURA	CONCLUSIONI
DISTIROIDISMO (subclinico):	Circa 150 studi	Concorde per occasionali casi di tireotossicosi Controversa per i subclinici
INFEZIONI	Circa 450 studi	Concorde per le infezioni acute (aborto occasionale) Possibile ruolo della Clamydia nell'aborto ricorrente
PCO Resistenza all'insulina Diabete	Circa 300 studi	PCO isolata: molto controversa Insulino Resistenza: piuttosto riconosciuta Diabete (solo se fortemente scompensato. Acidosi)
CELIACHIA	Meno di 20 studi	Molto incerta. Alcune segnalazioni riferiscono di un aumento del rischio di aborti ripetuti nei celiaci con HLA DQ2/DQ8 positivo

Gabbe: Obstetrics, 6th ed. - 2013 - Churchill Livingstone, Elsevier
ESHRE, 2017

What to do?

Making a diagnosis of abortion by:

Clinic

Ultrasonography (morphology)

Histology

Genetics

Micro-Abortion
(pre-clinical miscarrage)

Biochemically dubious

This is a "suspect" abortion. It is more consistent in PMA. They are generally repeated

- First, or immediately after, the interaction phase with the stroma (adhesion) but not integration.
- Biochemically dubious (generally hCG testable fleetingly)
- Ultrasound is not evident
- Histologically generally not investigable
- Genetically maybe investigable with fetalDNA

Blasto defect:

- Hatching defect
- Integrin defects and trophoblastic proteins
- Lack of interaction with the stroma

Blasto defect:

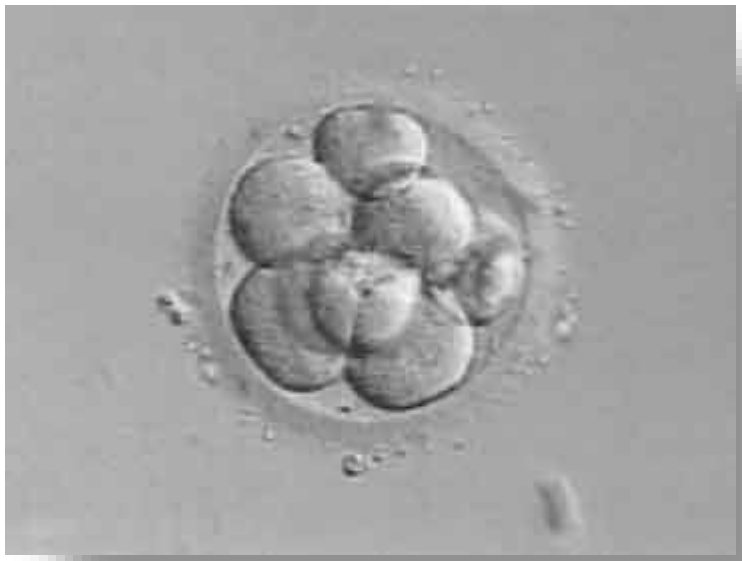
Genetic factors are usually responsible for ovular abortion.

No vascular structures develops.

More than 80 percent of first-trimester spontaneous abortions are genetic [(1)].

Autosomal trisomies comprise the largest (approximately 50 percent) class of chromosomal complements in cytogenetically abnormal spontaneous abortions. Trisomy for every chromosome except chromosome 1 has been reported, and trisomy for that chromosome has been observed in an eight-cell embryo.

The most common trisomy is trisomy 16.

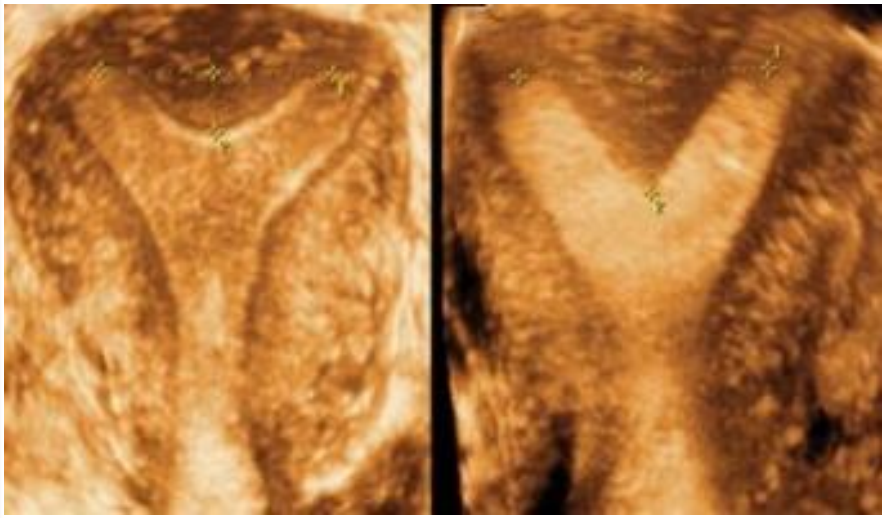


1: Additional information from chromosomal microarray analysis (CMA) over conventional karyotyping when diagnosing chromosomal abnormalities in miscarriage: a systematic review and meta-analysis. Review article Dhillon RK, et al. BJOG. 2014. Authors Dhillon RK1, Hillman SC, Morris RK, McMullan D, Williams D, Coomarasamy A, Kilby MD.

Implantation area defect:

- Malformations lack interaction / integration with the stroma (from absolute vascular defect of the implant area: utero septum avascular)
- if the invasion occurs but not the interaction with the stroma the test rarely can result positive.

Implantation area defect:

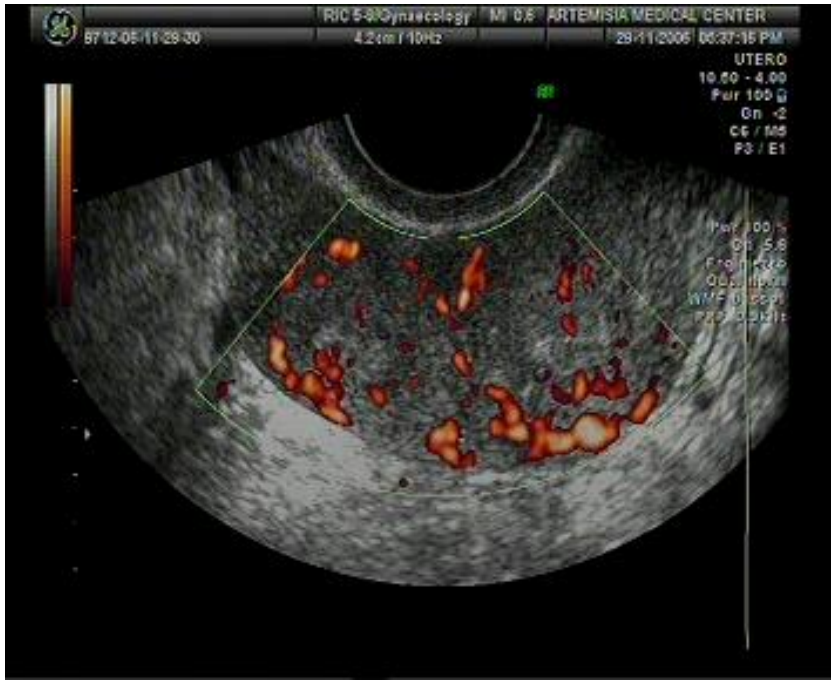


Small malformations bring more abortions:

arcuate P <0.01, compared with controls
septate P <0.01, compared with controls
bicornuate uterus P <0.05, compared with controls

Saravelos, *Reprod Biomed Online. 2010 Mar;20(3):416-422. Epub 2009 Dec 11.*

Implantation area defect:



The importance of vascularization
Double and complete vascularization

Implantation area defect:

•The prevalence of uterine anomalies in the general population was 1 in 201 women (0.50%).

•Uterine anomalies were identified in 1 in 594 fertile women (0.17%) and in 1 in 29 infertile women (3.5%). P < .00001).

•Their distribution was:

- 7% arcuate,
- 34% septate,
- 29% bicornuate,
- 11% didelphic,
- 5% unicornuate,
- 4% hypoplastic/aplastic/solid and other forms

Nahum *J Reprod Med. 1998 Oct;43(10):877-87.*

ABORTION

Si distinguono tre tipi di aborto:

- **occasionale**
- **ripetuto**
- **ricorrente**.

Si parla di **aborto ripetuto** quando, nella storia ostetrica di una donna, si verificano due episodi consecutivi di aborto entro la 20esima settimana di gravidanza. Questa condizione si riscontra in circa l'1% delle coppie in età fertile.

L'aborto ricorrente è, invece, definito come la presenza di tre o più episodi consecutivi di aborto spontaneo.

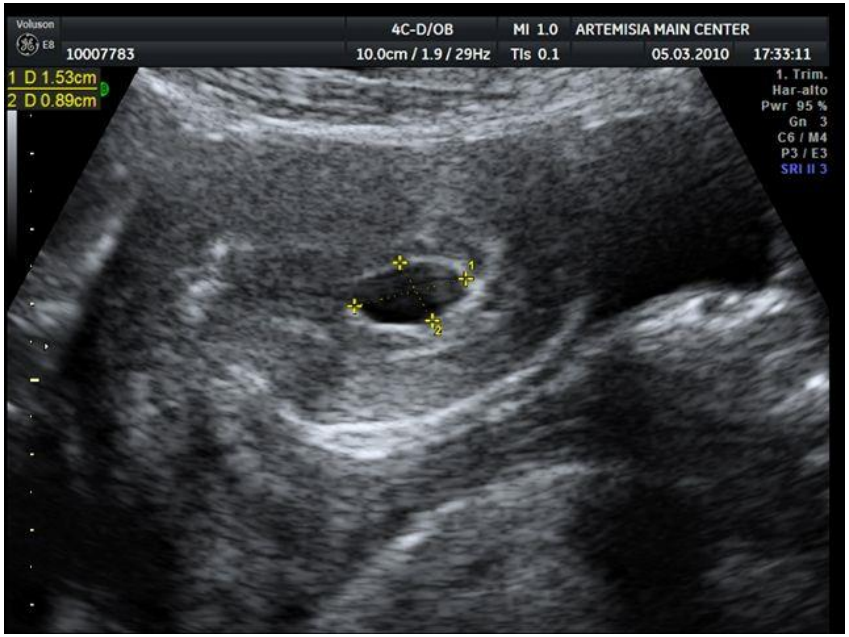
Attualmente, si parla genericamente di poliabortività e si attua uno screening in tal senso a partire dal secondo episodio consecutivo di aborto.

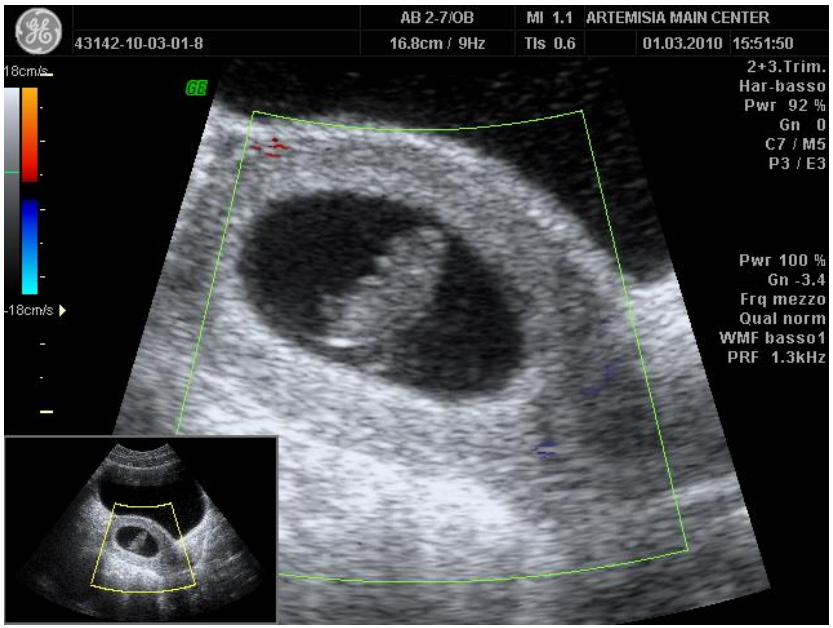
It is an abortion that occurs after implantation.
Most often occasional
Biochemical and US positive

Biochemically heterogeneous (hCG low or high at the beginning)
Ultrasound no embryo or embryo
Histologically heterogeneous and informative
Genetically heterogeneous and informative

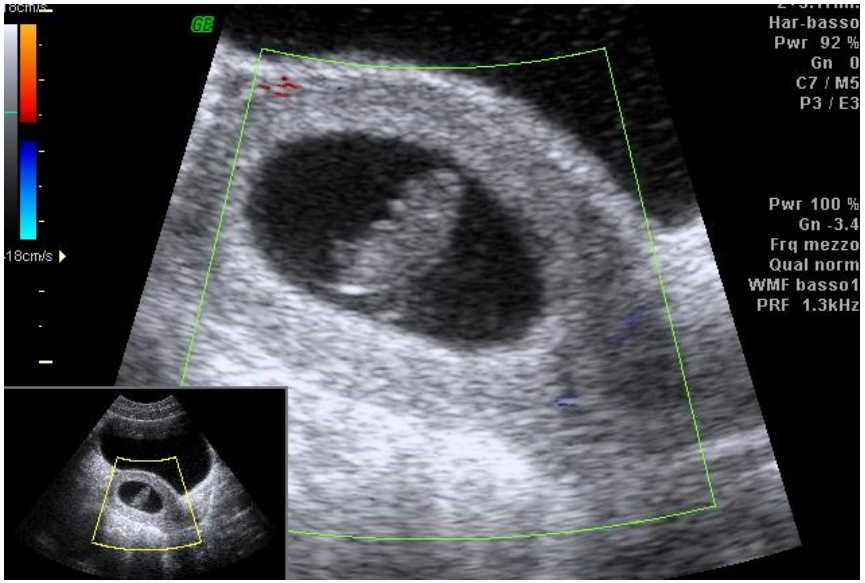
NB: before making a diagnosis of infertility from **recurrent abortion it is important to verify that the type of abortion has the same characteristics and that it is not**, on the contrary, unlike abortions, in this case it is possible that occasional abortions have been repeated (bad luck)

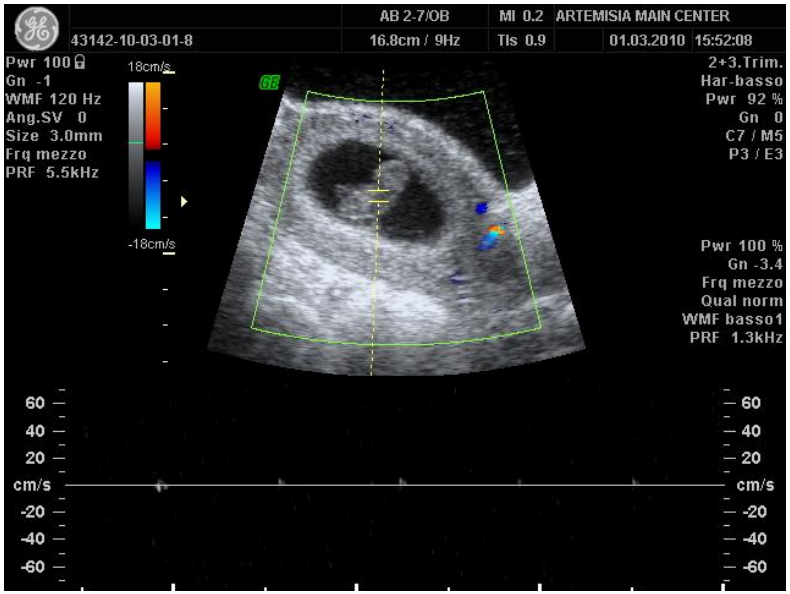
But abortions are all the same?





And all equal abortions, recognize the same cause?





FROM HYSTOLOGY TO THE ETIOLOGY

- **hydatidiform moles** (triploid),
- **villous dysmorphic features**: suggesting fetal aneuploidy,
- **chronic histiocytic intervillositis**: suggesting associated autoimmune diseases
- **massive perivillous fibrin deposition**: suggesting primary antiphospholipid antibody syndrome (PAPS)
- **impaired trophoblast invasion** decreased number of syncytio-vascular membranes: suggesting a genetic/vascular defect .
- **thrombosis, acute atherosis, suggesting an** arteriopathy in placentae from aPL positive patients.
- **trophoblastic hypoplasia**: suggesting genetic origin
- **stromal edema**, or cavitation: suggesting genetic origin
- **Fetoplacental hydrops:** suggesting genetic origin

CONCLUSION: Routine histological examination of products of conception in the setting of recurrent spontaneous abortion can provide important clinical information.

Placental pathology of recurrent spontaneous abortion: the role of histopathological examination of products of conception in routine clinical practice: a mini review (12 studies).
Jindal P, Regan L, e coll **Hum Reprod**. 2007 Feb;22(2):313-6. Epub 2006 Sep 27.
.
Placental pathology in antiphospholipid syndrome.
Levy RA, Avvad E e coll **Lupus**. 1998;7 Suppl 2:S81-5

FROM HYSTOLOGY TO THE ETIOLOGY

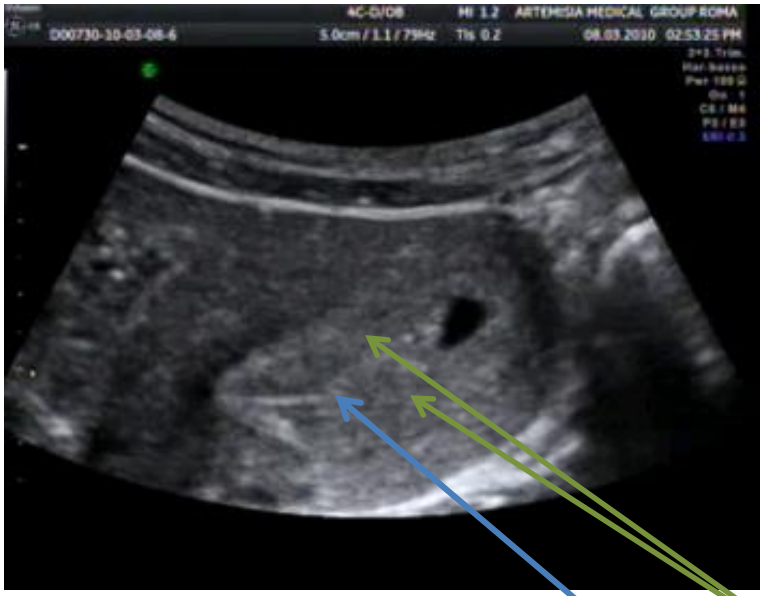
The NICE guideline on ectopic pregnancy and miscarriage recommends in Dec 2014 histopathology esamnation

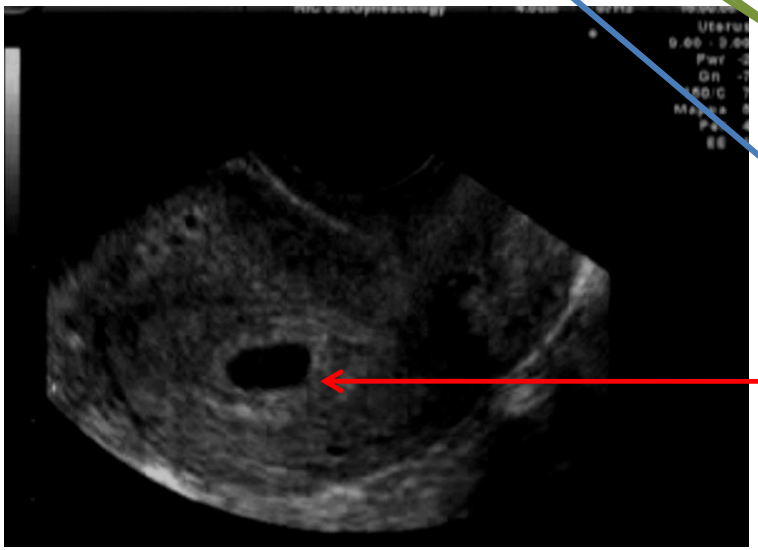
The Royal College of Pathologists "Tissue pathway for histopathological examination of the placenta“ in miscarrage

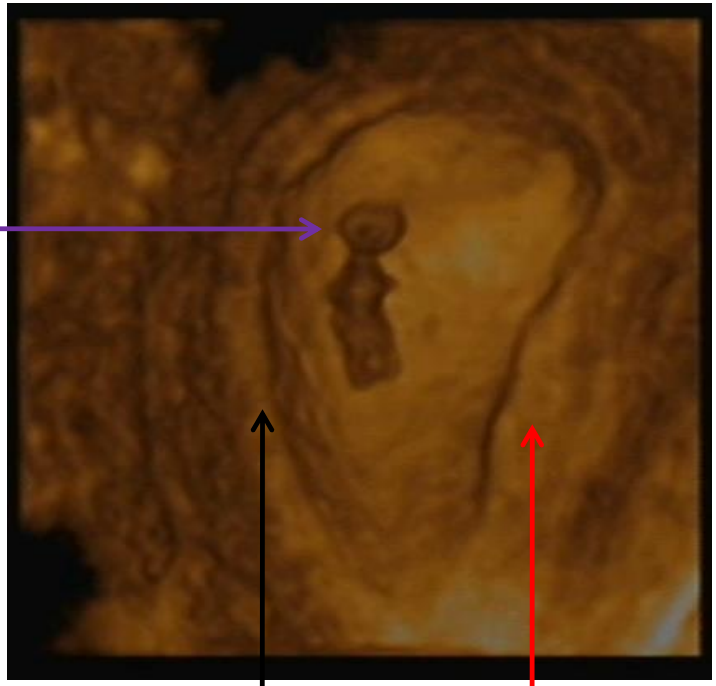
From ultrasound the etiological suspicion

In the ultrasound diagnosis of abortion:

1. Consider all the characteristics.
2. Collect medical history
3. Compare, if there were other abortions (where possible) the images.
4. Request Kariotype
5. Request accurate histological examination







Yolk

Decidua

Chorion laeve

Cavity echo

Chorion frondosum

Genetic miscarrage

COMPLETION	FREQUENCY	PERCENT
Normal 46,XX or 46,XY		54.1
Triploidy		7.7
69,XXX	2.7	
69,XYX	0.2	
69,XXY	4.0	
Other	0.8	
Tetraploidy		2.6
92,XXX	1.5	
92,XXYY	0.55	
Not Stated	0.55	
Monosomy X		18.6
Structural abnormalities		1.5
Sex chromosomal polysomy		0.2
47,XXX	0.05	
47,XXY	0.15	
Autosomal monosomy (G)		0.1

COMPLETION	FREQUENCY	PERCENT
Autosomal trisomy for chromosomes		22.3
1	0	
2	1.11	
3	0.25	
4	0.64	
5	0.04	
6	0.14	
7	0.89	
8	0.79	
9	0.72	
10	0.36	
11	0.04	
12	0.18	
13	1.07	
14	0.82	
15	1.68	
16	7.27	
17	0.18	
18	1.15	
19	0.01	
20	0.61	
21	2.11	
22	2.26	

Genetic etiology

PRE- CLINICAL and CLINICAL ABORTION UNITARY THEORY OF GENETIC SELECTION

85 % of aborted fetuses present chromosomal and subcrhomosomal abnormalities

- **Additional information from chromosomal microarray analysis (CMA) over conventional karyotyping when diagnosing chromosomal abnormalities in miscarriage: a systematic review and meta-analysis. Review article Dhillon RK, et al. BJOG. 2014. Authors Dhillon RK1, Hillman SC, Morris RK, McMullan D, Williams D, Coomarasamy A, Kilby MD.**
- Comparison of cytogenetics and molecular karyotyping for chromosome testing of miscarriage specimens. Shah MS, et al. Fertil Steril. 2017.
- Informatics enhanced SNP microarray analysis of 30 miscarriage samples compared to routine cytogenetics. Lathi RB, et al. PLoS One. 2012. Authors Lathi RB1, Massie JA, Loring M, Demko ZP, Johnson D, Sigurjonsson S, Gemelos G, Rabinowitz M.
- Diagnostic utility of microarray testing in pregnancy loss. Rosenfeld JA, et al. Ultrasound Obstet Gynecol. 2015. Authors Rosenfeld JA1,2, Tucker ME3, Escobar LF3, Neill NJ1,2, Torchia BS1, McDaniel LD1, Schultz RA1, Chong K4, Chitayat D4.
- Traditional karyotyping vs copy number variation sequencing for detection of chromosomal abnormalities associated with spontaneous miscarriage. Liu S, et al. Ultrasound Obstet Gynecol. 2015. Authors Liu S1, Song L1, Cram DS2, Xiong L1, Wang K1, Wu R1, Liu J3, Deng K1, Jia B1, Zhong M1, Yang F1

Abortion due to a genetic **imbalancement imprinting**

Imprinting biological principle:

- Maternal Genes start develops embryo
- Paternal Genes start develops Throfoblast

Nature 1990

In consequence:

Androgenetic zygotes 2n chromosomes ALL of male derivation:
abortive embryos with hyperplasia of the trophoblast, almost no embryo

Gynogenetic zygotes 2n chromosomes ALL of female derivation:
abortive embryos with almost non-embryonic structures almost absent, almost normal embryo

Abortion due to a genetic **imbalancement imprinting**

The paternal and maternal genomes have, at the beginning, different purposes on chorion-embryo organization.
The **paternal** is more important for the development of extraembryonic tissues (placenta and sack of yolk),
The **maternal** one for fetal tissues.
(The paternal genome is relatively more important for the development of extraembryonic tissues, and the maternal genome contributes more to fetal development. **Surani,** Nature 1994).

In previous experiments it had been shown that:

A) if a maternal pronucleus with two paternal ones is substituted: **androgenetic zygotes** develops a large placenta and no embryo.

B) if a paternal pronucleus is substituted with two maternal ones: **gynogenetic zygotes** develops an embryo that soon dies because there is not enough corial tissue.

Mc Grath Cell 1984

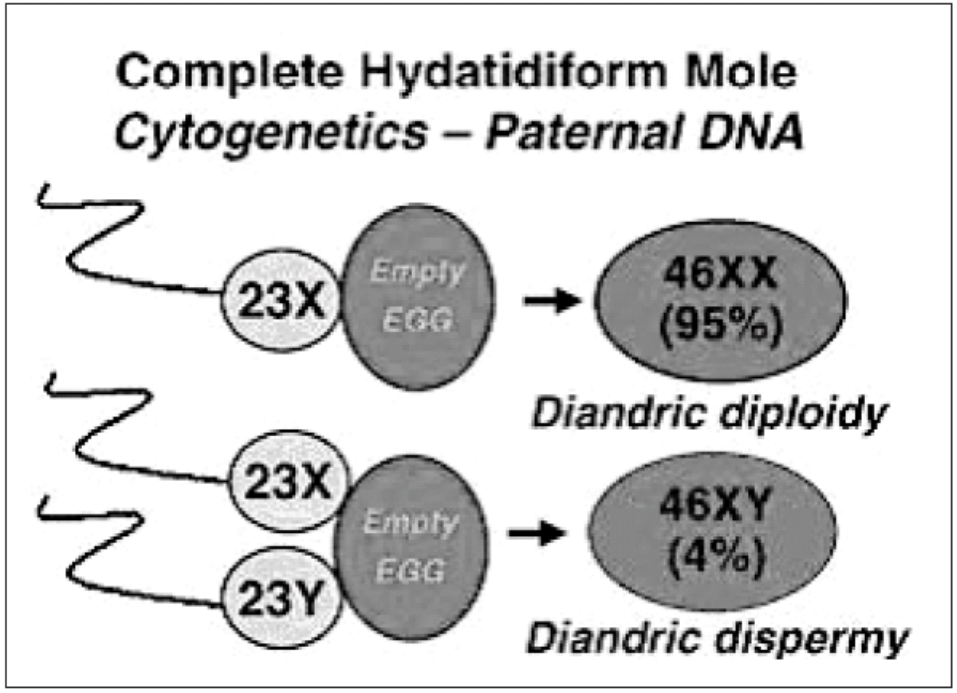
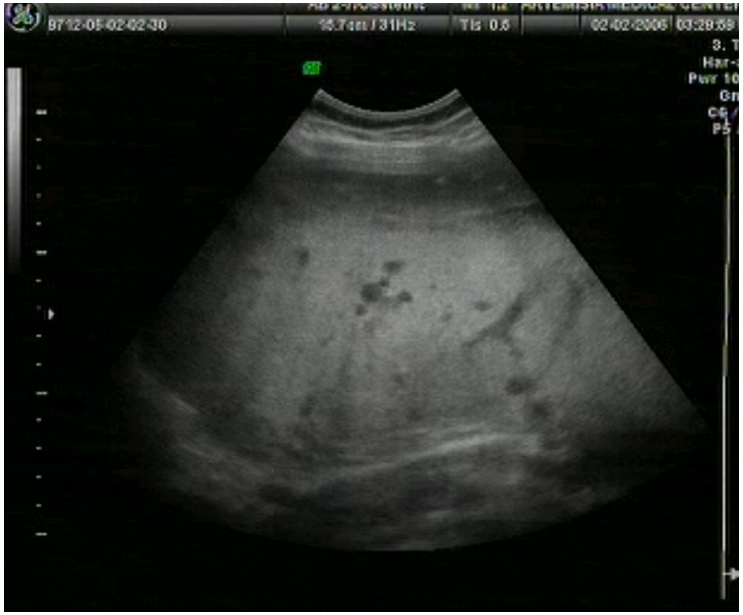
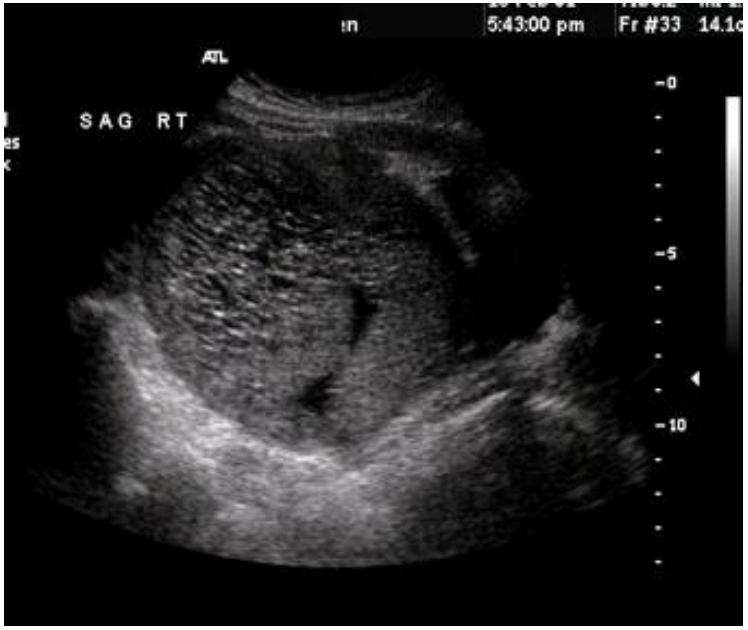


Figura 5.14 - Immagine raffigurante le varianti eziopatogenentiche della mola idatoforme completa.





The absence of the maternal genetic heritage is responsible for the absence of the embryo.

The complete mole are diploid and with only paternal nuclear DNA.

1. fertilization of an egg, in which the maternal genetic heritage is lost, by a spermatozoon that duplicates its own (complete androgenetic vesicular mola). 90% of complete wheels (homozygotes).
2. Disperm fertilization of an empty egg: this mechanism represents about 5-10% of the complete (homozygous) wheels.

NB: the 46YY form, theoretically possible, never reported (not vital).

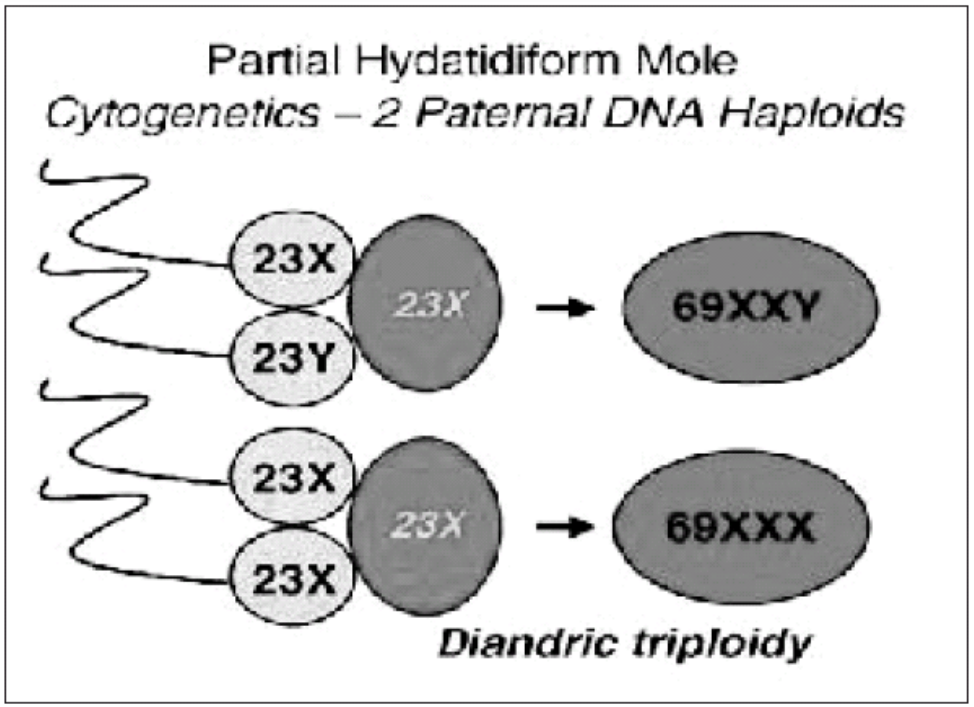
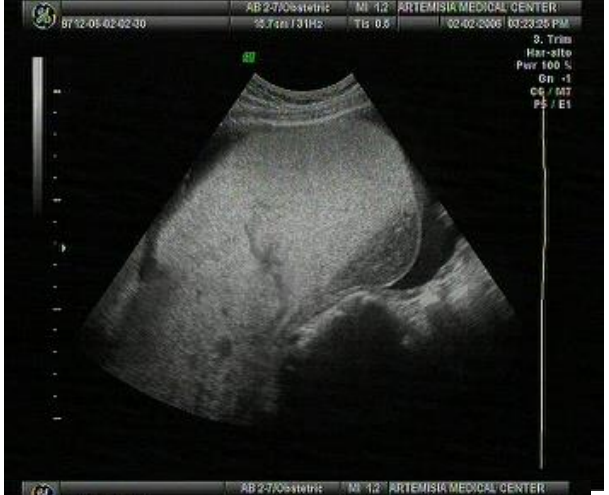
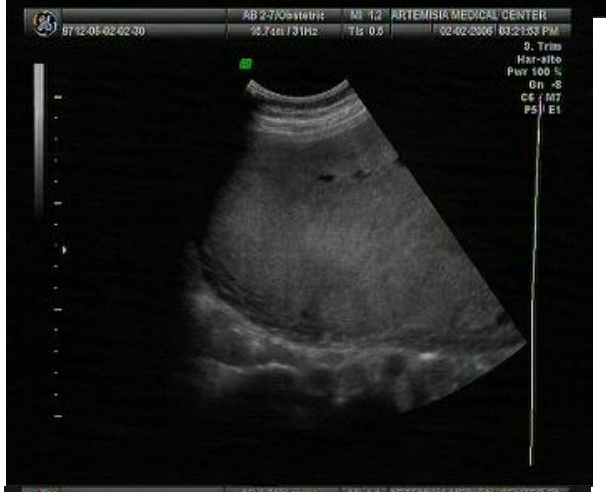
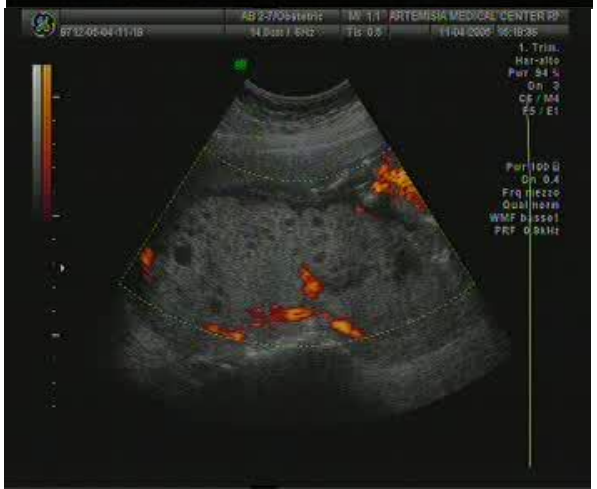


Figura 5.15 - Aspetti eziopatogenentici della mola idatiforme parziale.







The partial mole is triploid (69 chromosomes), which results from the fertilization of an oocyte by means of either a duplicated sperm or two spermatozoa.
Of these, 70% are 69, XXY; 27% are 69, XXX and 3% are 69, XYY.
Not all triploid conceptions hesitate in partial grinding: in fact the triploid with two maternal sets does not have molar characteristics.

NB: The presence of the maternal chomosome mitigates the molar effects of the two paternal and makes possible the presence of the embryo or fetus.

Genetic etiology

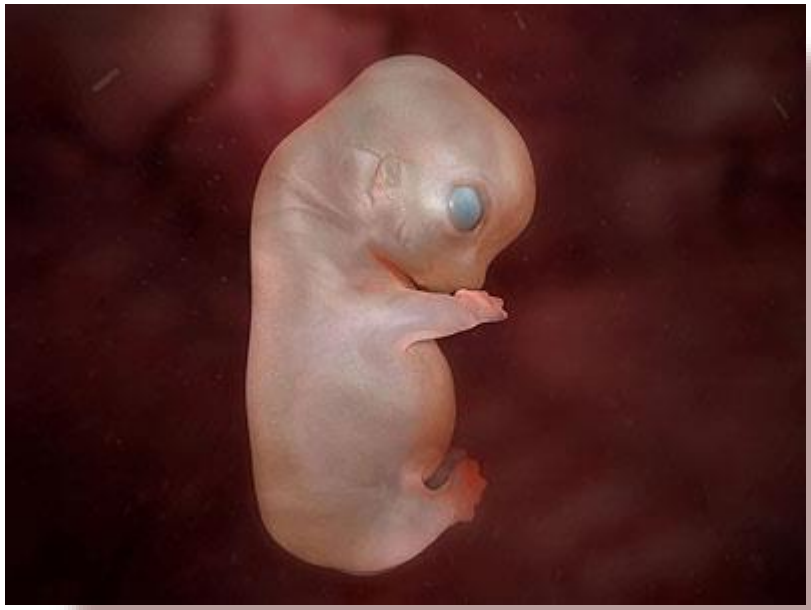
THE BEHAVIOR OF VILLUS:
The genetic pathology is accompanied by villi that do not divide and do not attack the trophoblast. Being a fetal problem (postplacental) of early origin it is accompanied by an NO-BRANCHING angiogenesis.

Genetic etiology

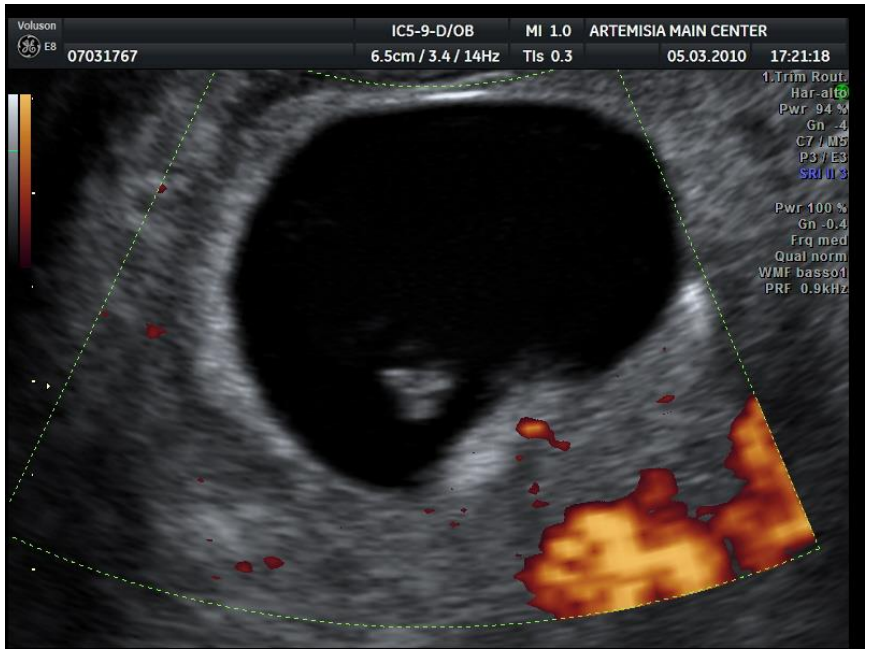
THE EMBRYO MORFOLOGY:

Various attempts have been made to correlate morphologic abnormalities with specific trisomies, but relationships are imprecise. Trisomies incompatible with life predictably show slower growth than trisomies compatible with life (trisomies 13, 18, and 21).

For example, the mean crown-rump length in abortuses shown to be trisomic (13, 18, and 21) is 20.65 mm compared with only 10.66 mm for trisomies that virtually never survive to term (e.g., trisomy 10 or 16



8 weeks. Asymptomatic, Small embryo. Lot of Yolk, thin Trofoblast, NO hemorrage or hematomas or abruptio



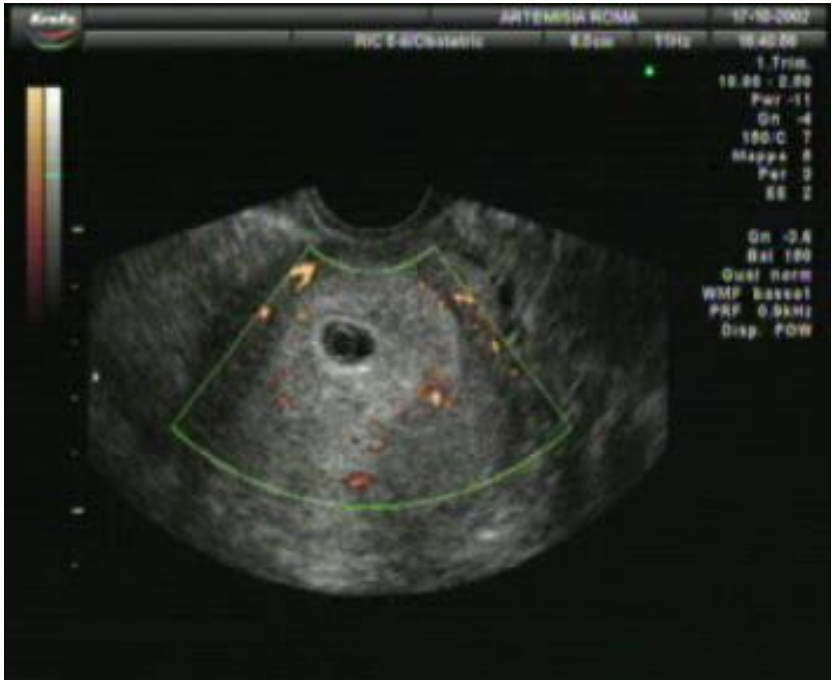
Eko:

- Absence of abnormalities of the uterine fund

- Embryonic pole presence
- small Yolk bag
- **Scarcity of the trophoblast (thin)**
- Absence of hematomas and / or detachments

Hypothesis: abortion from **maternal gene imbalance?**

9 weeks. Asymptomatic, No embryo, Relative large Yolk sac, Exuberant Chorion, clearly separated from decidua, often (round trophoblast) NO detachment.

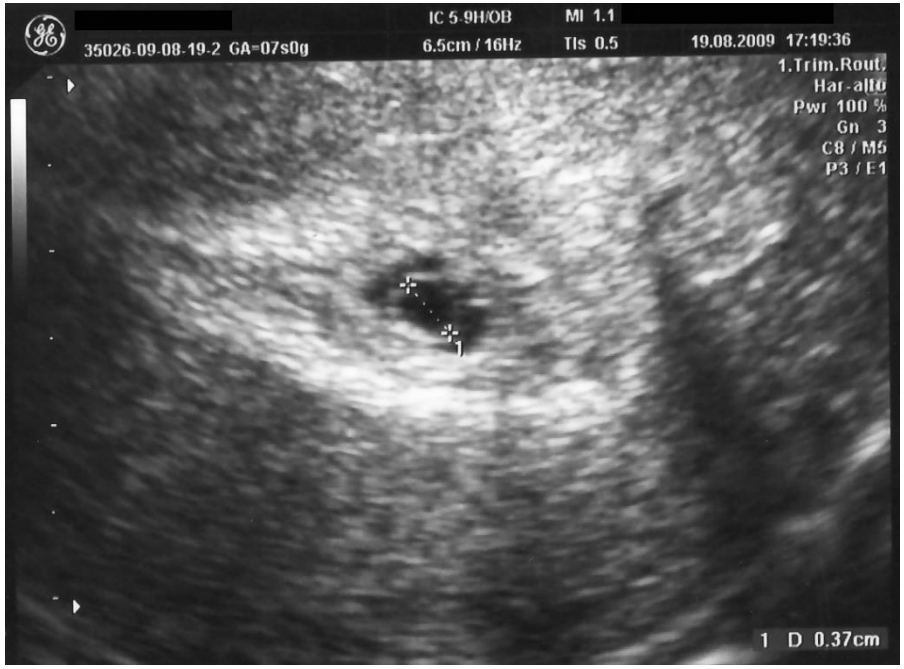


Eko:

- Absence of abnormalities of the uterine fund
- **Abundant well-defined trophoblast**
- Embryo absence
- Disproportion of yolk sac / gestational sac
- Absence of hematomas and detachments

Hypothesis: abortion from **paternal gene imbalance?**

The **gestational/yolk sac ratio**
provide useful prediction of the major chromosomal defects.



- in **trisomy 21** no differences with normal embryos
-In **trisomy 13** and triploidy, the small GSV.
- In **trisomy 18**, an increase in GSV.
- in **16 trisomy** usually small and large/dismorphic Yolk sac (see left picture)

Gestational sac volume measured by three-dimensional ultrasound: relation to chromosomal defects.
-Falcon and coll. **Ultrasound Obstet Gynecol.** 2005 Jun;25(6):546-50.

A yolk sac diameter out of two standard deviations of the mean for the menstrual age allowed prediction of an abnormal pregnancy outcome with a sensitivity of 65%, a specificity of 97%, a positive predictive value of 71%, and a negative predictive value of 95%.

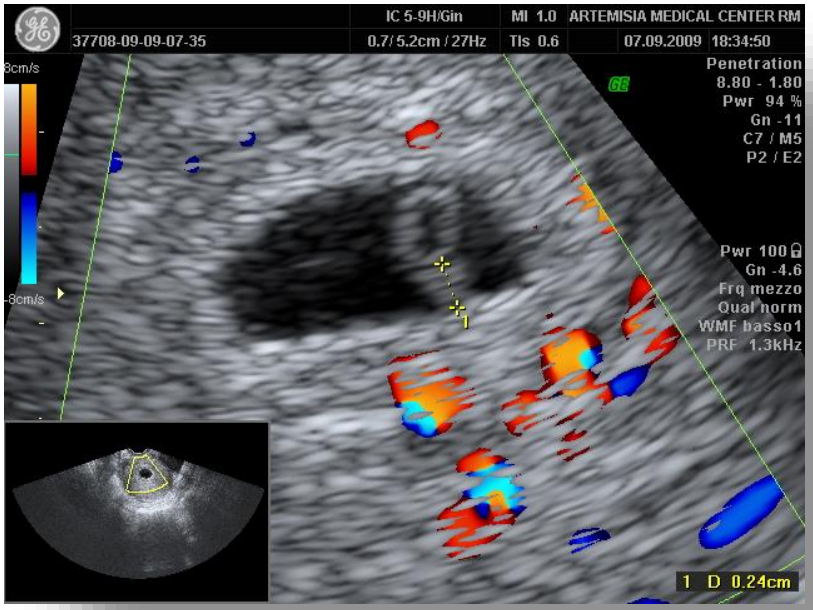
Yolk sac size and shape as predictors of poor pregnancy outcome.
Küçük T, e coll **J Perinat Med.** 1999;27(4):316-20.

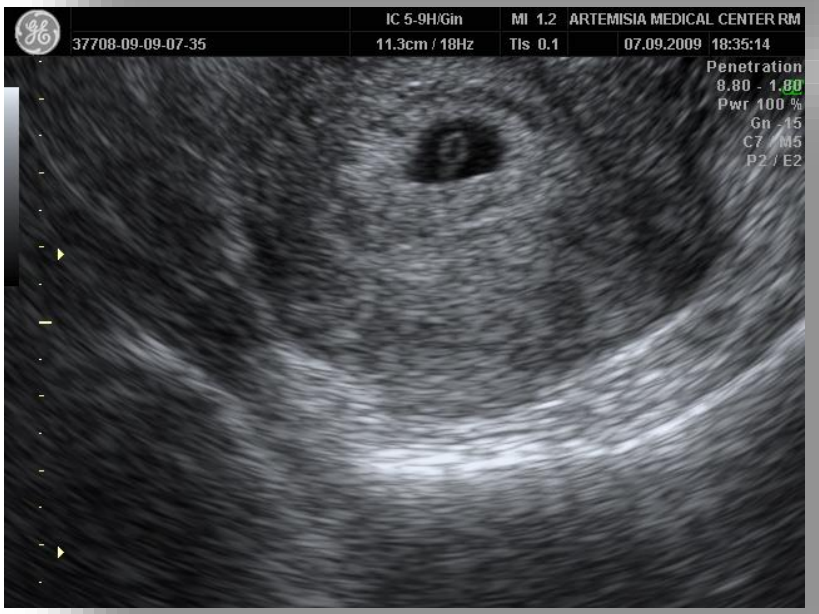
9 week. Asyntomatic

Eko:
Small gestational sac for the time.
Tiny embryo.
Regular Trofoblast well demarcated.
Lot of dysmorphic but hyperechogenic Yolk:

Abortive material **karyotype**: 47, XX, + 16

Histology: Presence of endometrial fragments in the deciduous transformation of the stroma in which there are areas of necrosis and acute inflammatory infiltrates. There are chorionic villi with hydropic degeneration in which some fetal blood cells are recognizable.





7 week: Asintomatic

Eko:

Large gestational sac

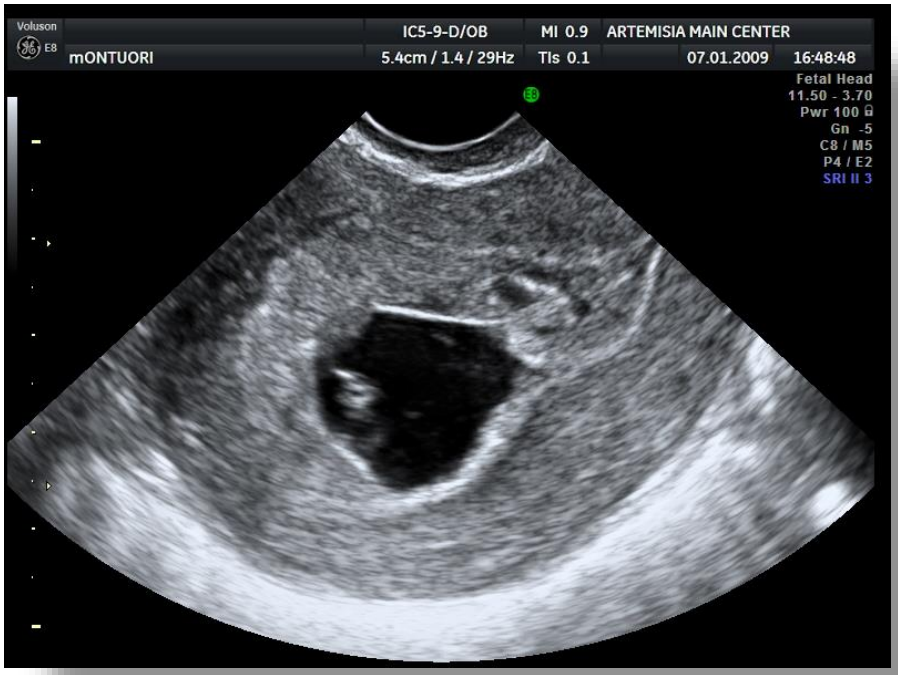
Trofoblast with hydrops

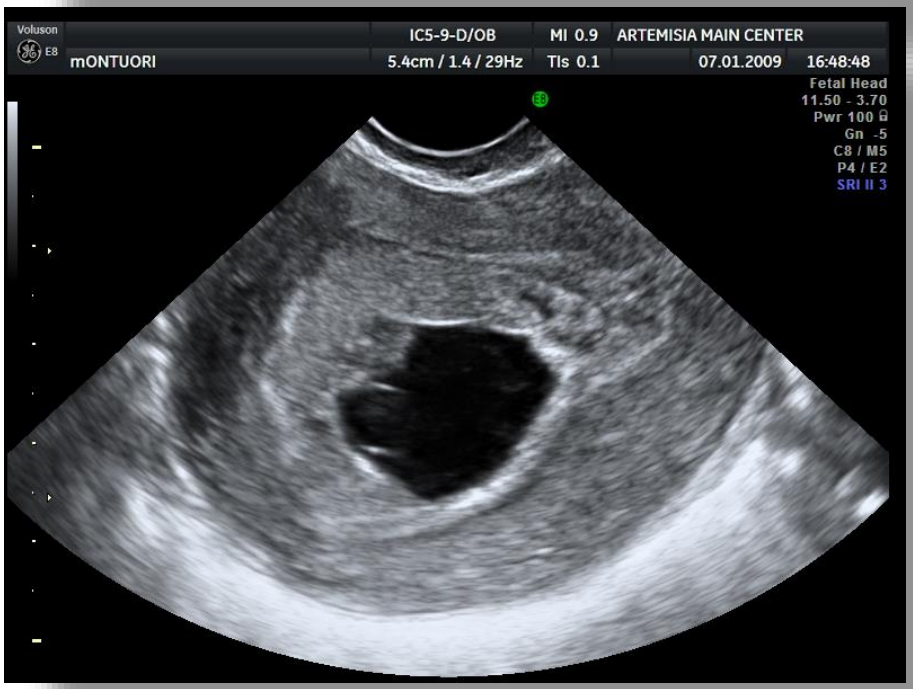
Large Yolk sac

Small and undervelopt embryo.

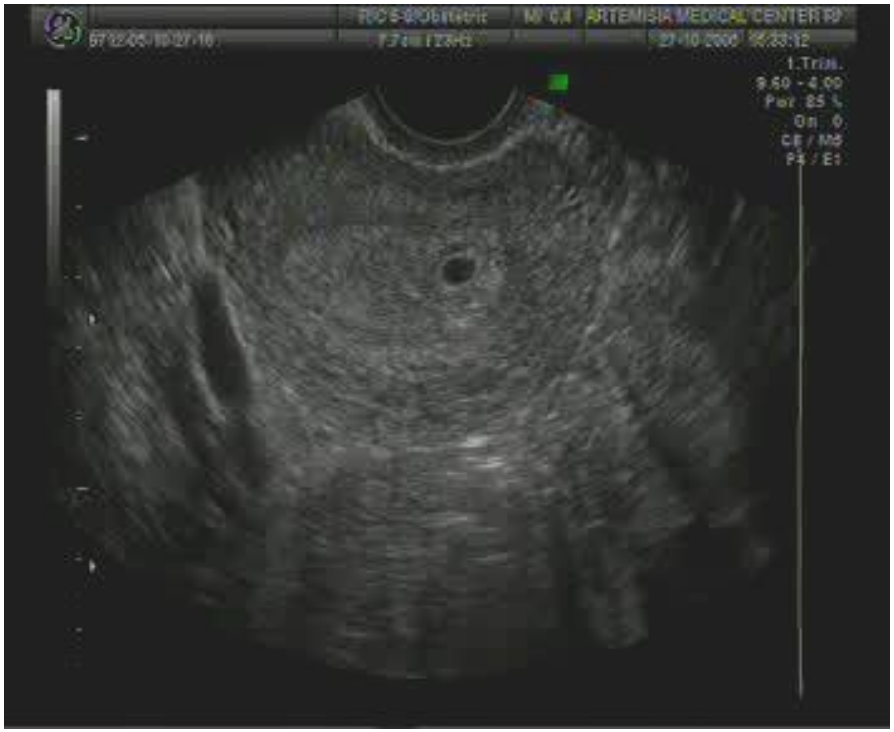
Cytogenetic

47 XY+18





8 weeks. Asymptomatic, No embryo, Small sac, sharp contours. Poor trophoblast. Exuberant gravidic decidua. NO detacment



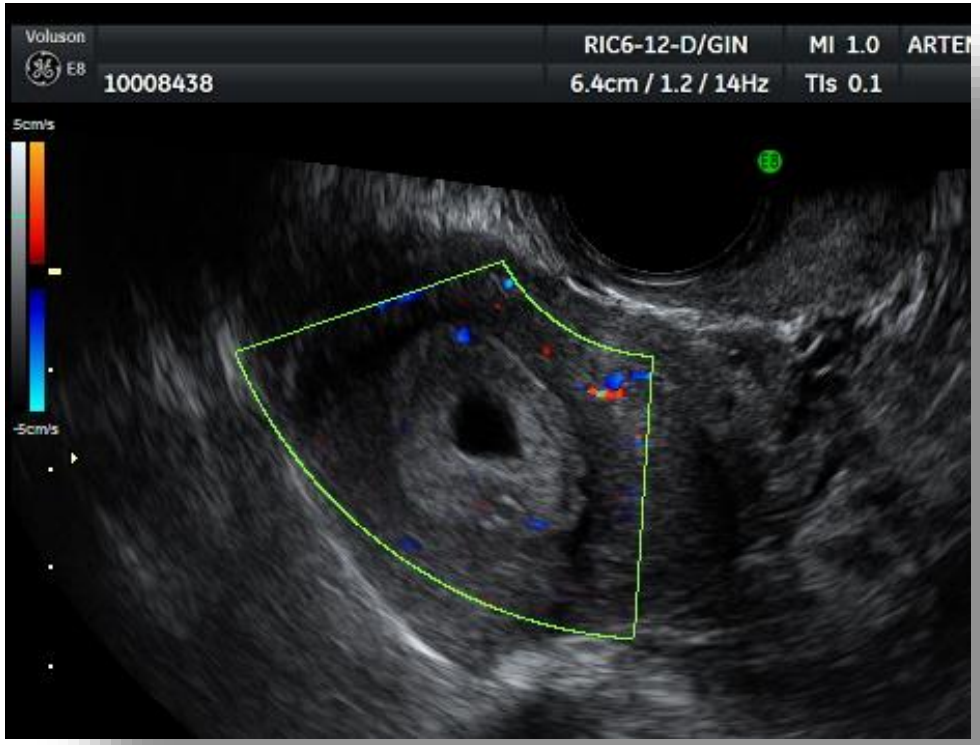
Eko:

- Absence of abnormalities of the uterine fundus
- Small gestational sac
- regular trophoblast
- Embryo absence
- Gestational age disproportion / gestational sac
- Absence of hematomas and detachments

Hypothesis: genetic abortion?

Diagnosis : 13 trisomy

8 weeks. Asymptomatic. No embryo. NO Yolk sac. The chorion frondosum is absent (subtle placenta). The sack is surrounded by a hyperechogenic trophoblast, well marked by the decidua.

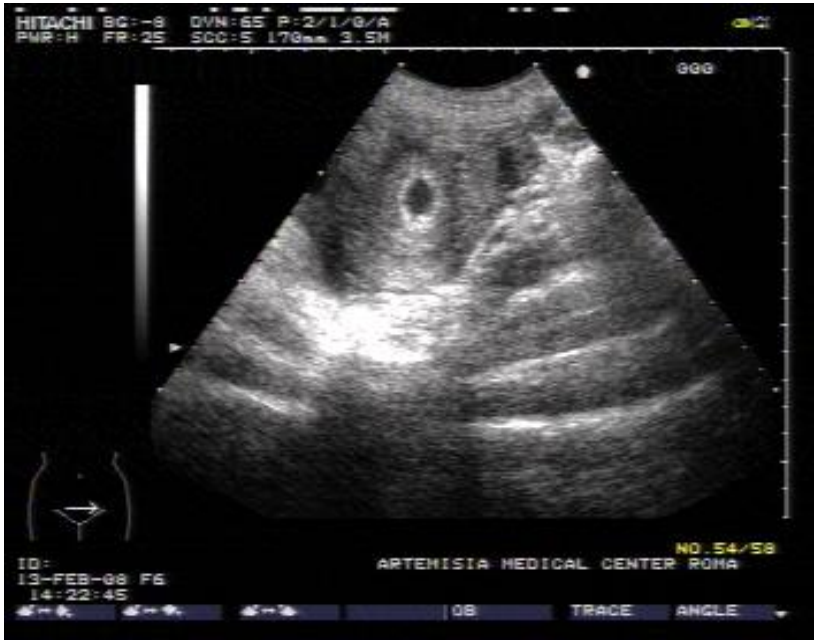


Eko:

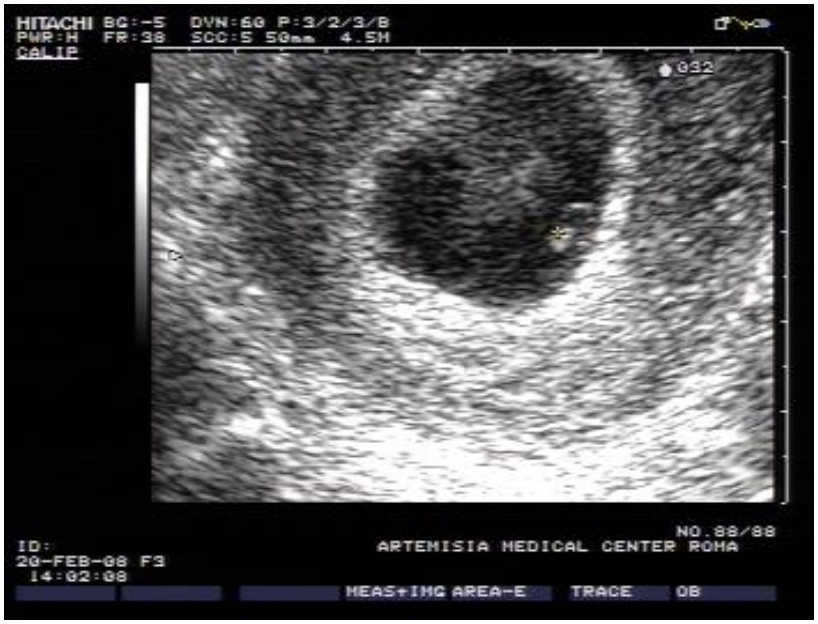
- Absence of abnormalities of the uterine fundus
- Absence of the embryonic pole depending on the time.
- Yolk sac not displayed
- Clear separation between decidua and trophoblast.
- Presence of an "excluded" trophoblast, demarcated, delimited, homogeneously echogenic.

-**Kariotype :** 47 xx +2

8 settimane. Asintomatico,



Eko: Regular gestational sac for the time.
Tiny embryo.
Trofoblast well demarcated.
Yolk sac more voluminous than the embryo pole:



Histology: Endometrium in the deciduous transformation of the stroma in which areas of necrosis are present. Scarce chorionic villi with hydropic degeneration.

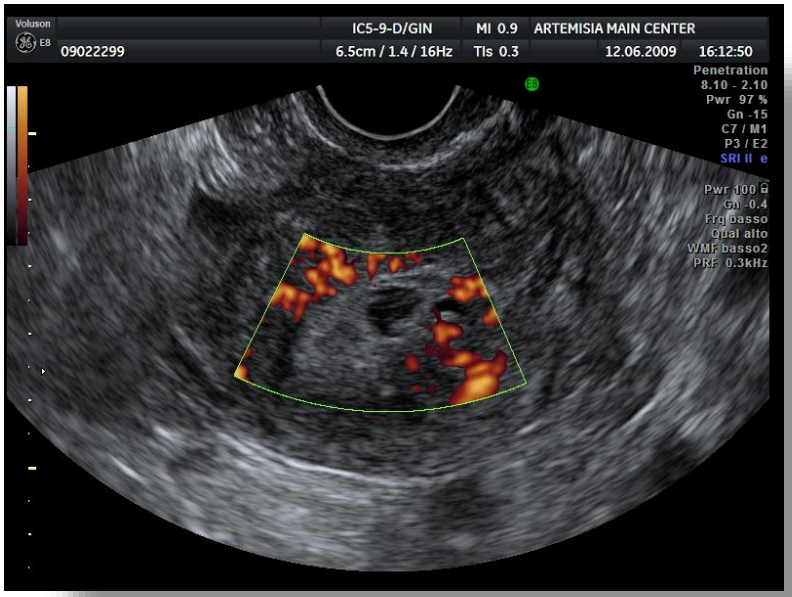
Abortive material **karyotype**: 47, XX, + 21

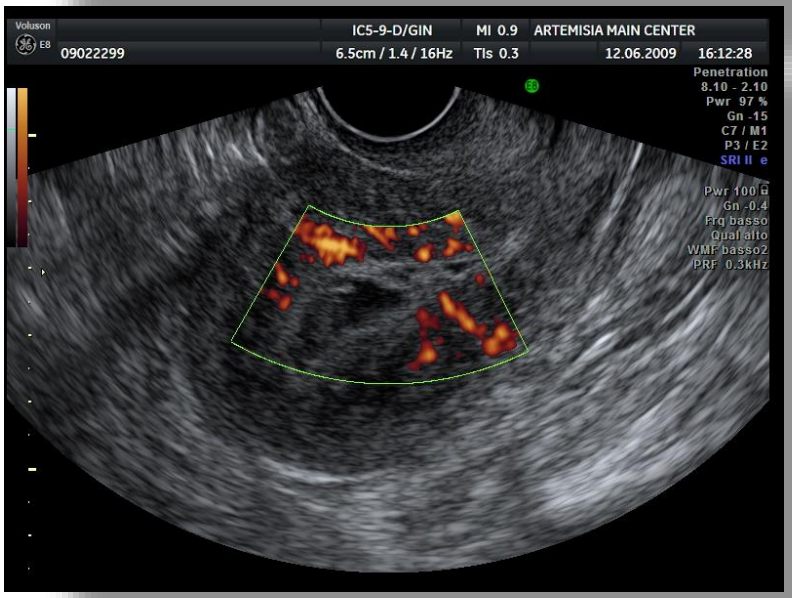
8 week. Asintomatic,

Eko: Small and dysmorphic sac.
No embryo,
Well-defined trophoblast.
Vacuolization (round trophoblast)
NO detachments

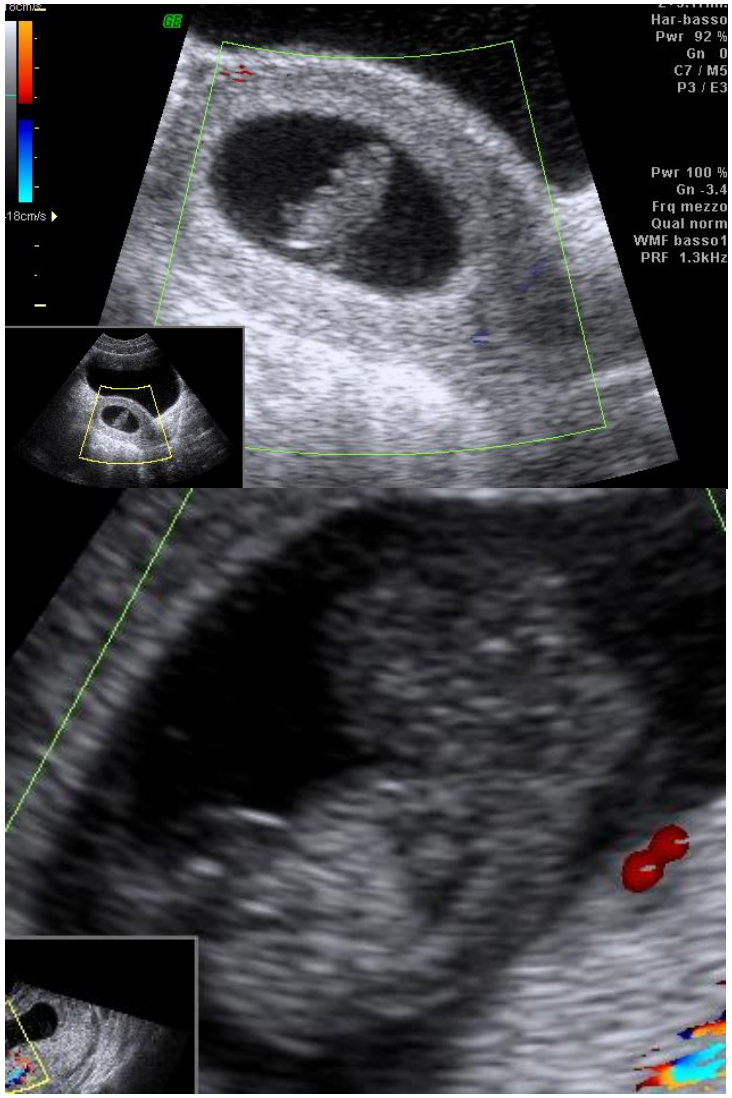
Histology: Necrotic and hemorrhagic deciduous-ovular material consisting of large decidua flaps
necrotic treatment of numerous chorionic villi with **hydropic and hypovascular stroma.**
They are repertory fetal red cells in the lumens of the villari vessels.
The tropoblast shows polar distrubution with evidence of some cytoplasmic vacatings.

Abortive material **karyotype:**
Triploid 69, XXX





11 weeks. Asymptomatic. Placenta well inserted. Absence of detachments. Good trophoblastization. Yolk regularly extraamniotic. Large amniochoric space.

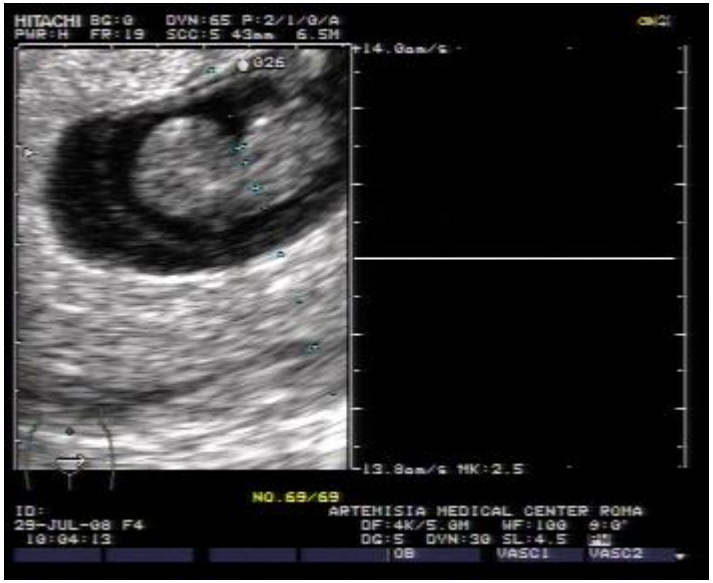


Eko:

- Uterine anomalies absent
- Normal insertion of gestational sac

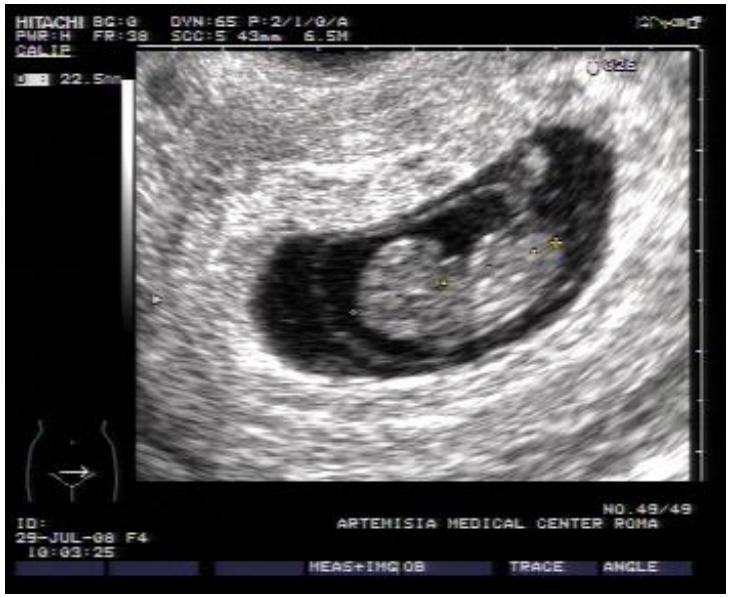
Hydrops and abnormal shape of the embryo.
(18 trisomy)

Young mather. First of 3 miscarage (10° week)



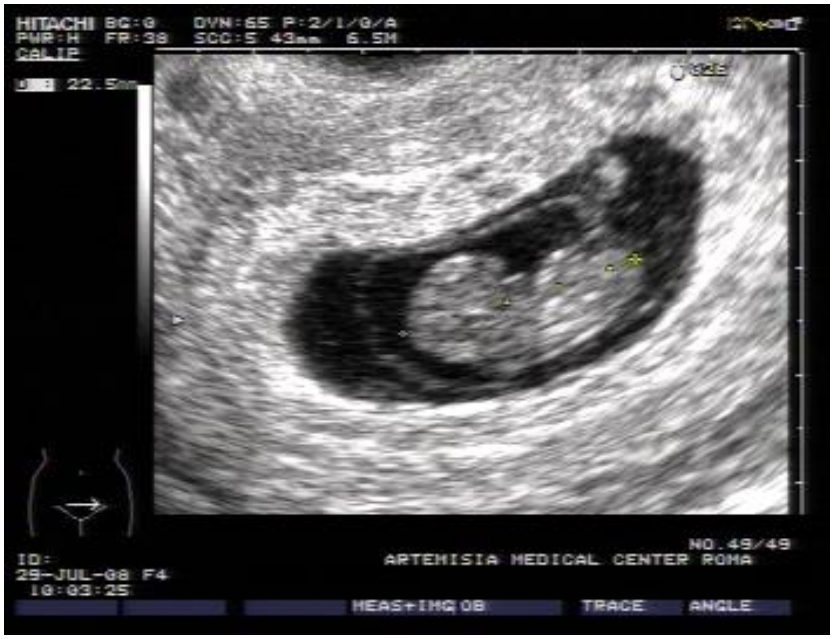
Eko: small amniotic sac with embryo attached large chorion-deciduous space.
NO detachment

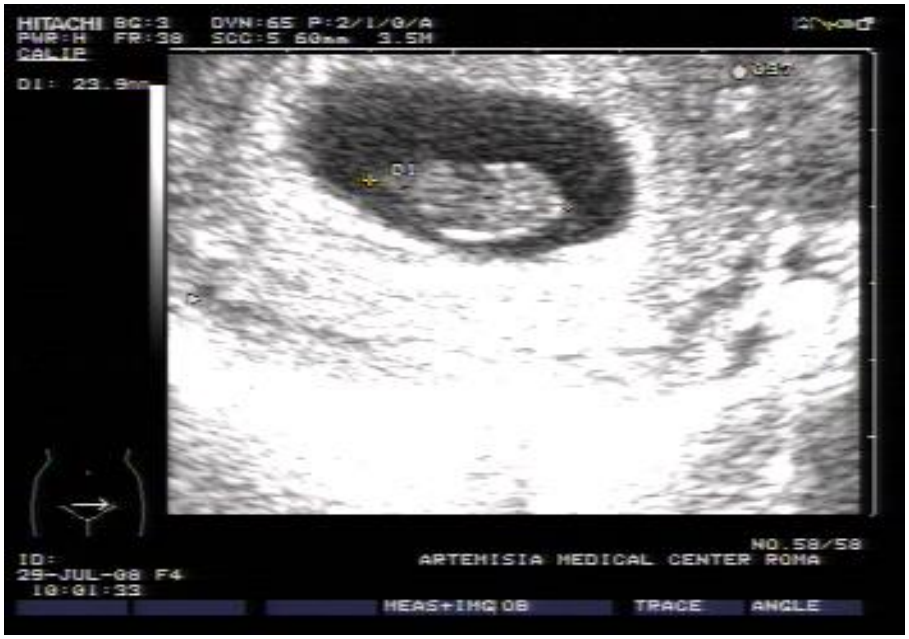
Histology: Necrotic and hemorrhagic deciduous-ovular material consisting of markedly hydropic chorionic villi in whose vessels fetal cells are found.
Also present are fragments of deciduous necrosis, which are associated with hypersecretory endometrium flaps.
Embryonic residues are identified.
The trophoblast shows small vacualizations of the cytoplasm and substantially polar distribution.



Cytogenetics: Abortive material 47 xx + 13

The same subject (two other ultrasound abortions similar histologically identical 2 trisomies of 13 and one of 18.)





Mutations in SYCP3, a gene encoding an essential component of the synaptonemal complex that is central to the interaction of homologous chromosomes, are associated with recurrent pregnancy loss. The mutation resulting in the production of C-terminally mutated proteins that interact with their wild-type counterpart and inhibit the normal fiber formation and generate an aberrant synaptonemal complex and contribute to abnormal chromosomal behavior that might lead to recurrent miscarriage

Mutations of the SYCP3 gene in women with recurrent pregnancy loss. Bolor H, Mori T, Nishiyama S, e coll **Am J Hum Genet. 2009** Jan;84(1):14-20. Epub 2008 Dec 24.

Uterine malformation

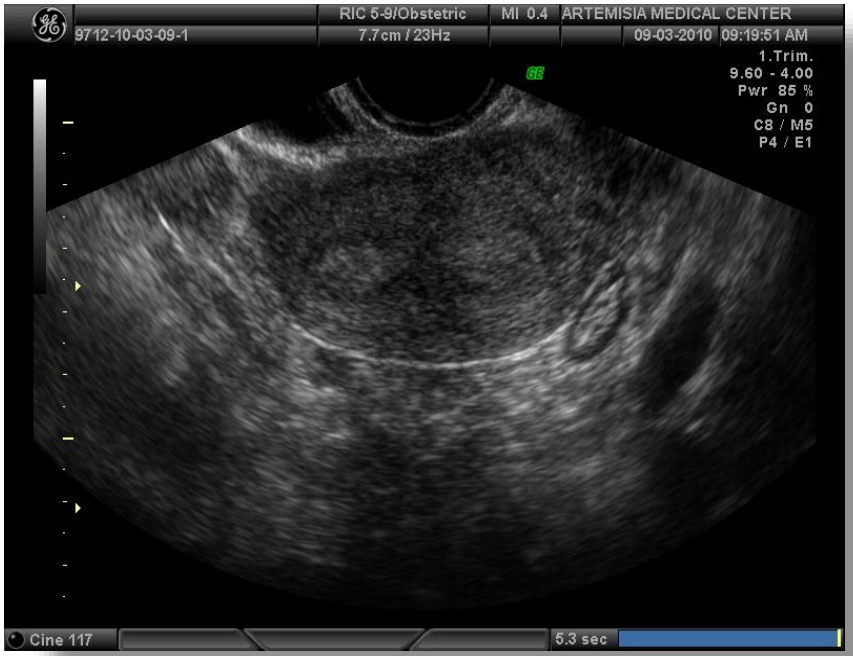
Usually early abortions:

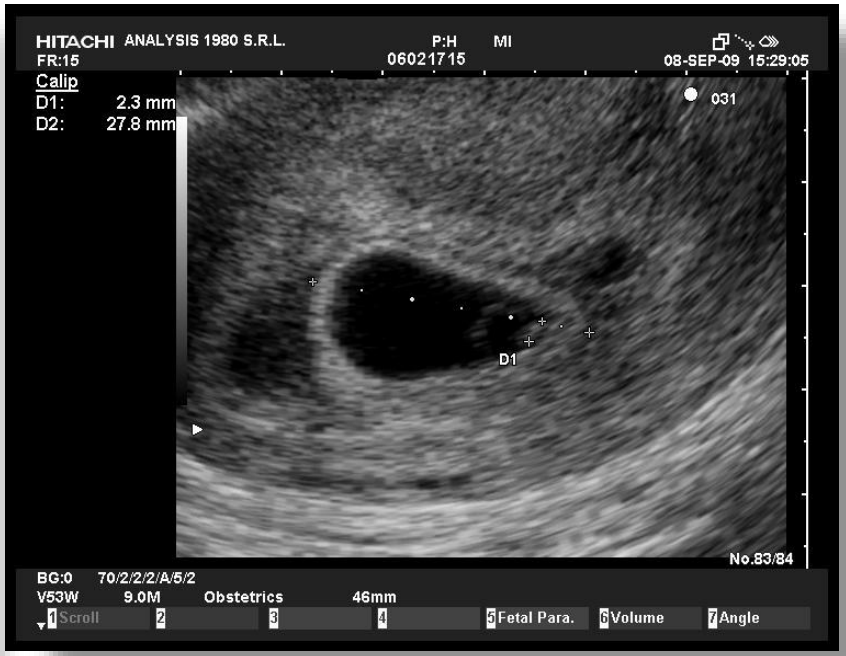
1 pregnancy: does not do therapy. Exam in abortion at 8 weeks (asymptomatic up to 12) performed 12-week review

- 2 pregnancy: progesterone and rest. Presents detachments. Suspends therapy at 16 weeks. Evolve and end with PS 3050

- **3 pregnancy:** performs progesterone but immediately results in 5-week abortion

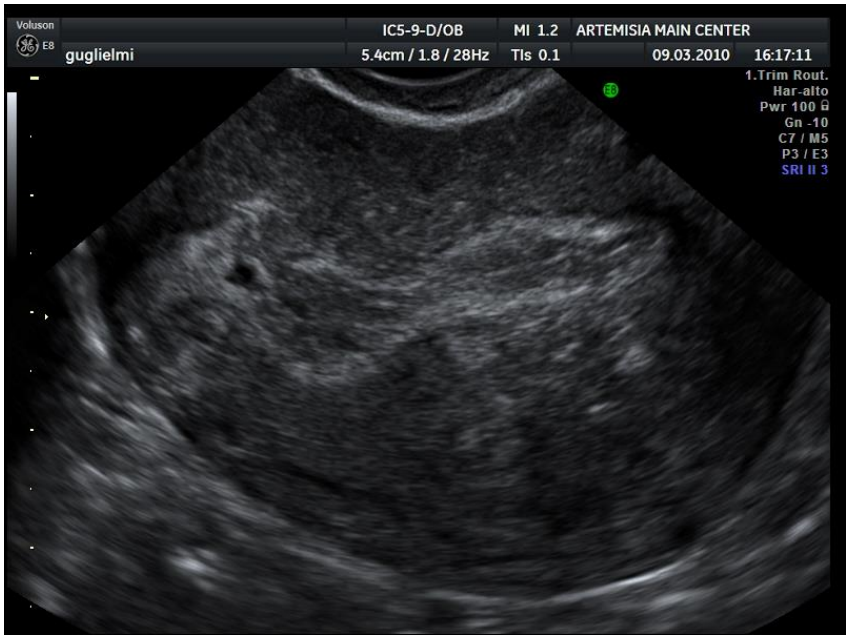
- **4 pregnancy:** Progesterone, heparin and cardioaspirin. In abortion at 8 weeks (bcf not perceived) small asymptomatic detachments. Histology not informative for infections and for chromosomopathy or thrombosis





- 5 pregnancy: Progesterone, heparin, cortisone and cardioaspirin. Abortion occurs at 8 weeks (perceived bcf) asymptomatic small detachments. Histology not informative for infections and for chromosomopathy or thrombosis

Anti Phosfolipidic Syndrome



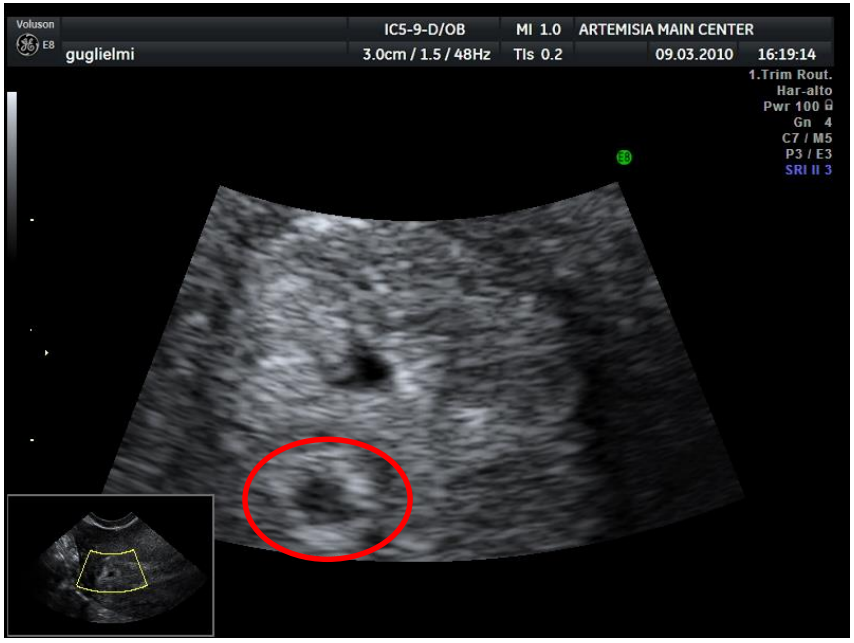
Subject to the 4th abortion:

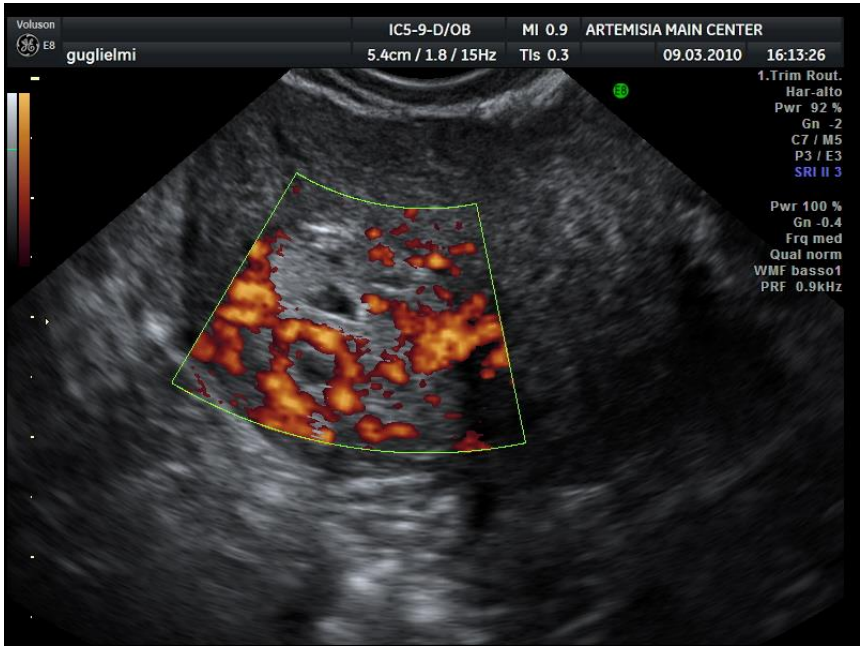
The hCGs grow rapidly until the sixth week, then they stop.

LAC ++ and elevated anticardiolipin

NB: Presence of an involute trophoblast, demologously echogenic. Irregular, badly delimited. Muffed crushed bag. The vases surround but do not enter the trophoblast.

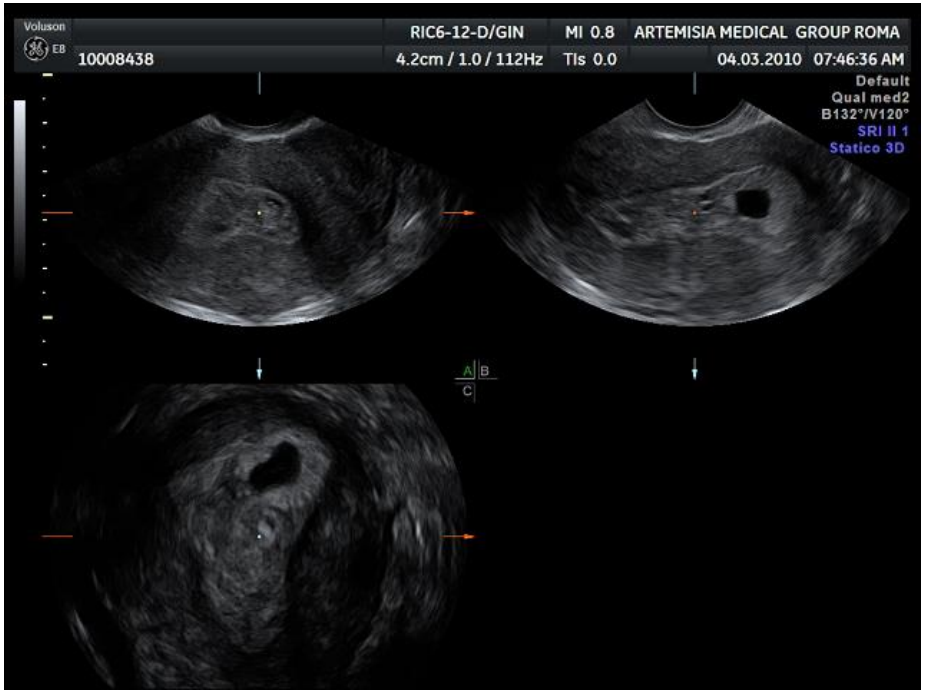
Classic small "echo ring"





Infection

10 weeks. Symptomatic (bleeding and pains). Dismorphic sac. Embryo present. Sack of Yolk. The chorion frondosum is surrounded by a thick gravidic, uneven lacunar gravid.
Microtrombi and microcavities
Histological examination shows inflammatory infiltrates and plasma cells



- Absence of abnormalities of the uterine fundus
  Dismorphic sac
  Typically late abortion
  Presence or absence of the embryonic pole depending on the time.
  Sacco Yolk present depending on the time
  Deciduous and trophoblast are confused, with anechoic areas, hyperechogenic deposits, small hematomas.

Hypothesis: abortion from an infectious cause?

What to do?

ESHRE GUIDELINES IN RPL (NOVEMBER 2017):

SCREENING GENETICI		
Cariotipo genitoriale	Entrambi	Sangue periferico eparinizzato
Test frammentazione DNA spermatico	Uomo	Liquido seminale 3/5 gg astinenza
SCREENING TROMBOFILIA ACQUISITA		
Anticorpi anti-fosfolipidi, Lupus Like anticoagulant (LAC), anti-cardiolipina (ACA IgG,IgM), anti-beta2 glicoproteina1	Donna	Sangue
FATTORI ENDOCRINOLOGICI		
Distiroidismo subclinico TSH, FT4, anticorpi anti-TPO	Donna	Sangue
SCREENING TROMBOFILIA EREDITARIA (facoltativa secondo le LL.GG.)		
Mutazione fattore V di Leiden, Mutazione della protrombina, Mutazione MTHFR, Resistenza alla Proteina C attivata, Dosaggio Proteina C attivata, Dosaggio proteina S attivata, Valutazione deficit ATIII	Donna	Sangue
CELIACHIA (facoltativa secondo le LL.GG.)		
Anticorpi anti transglutaminasi, anti gliadina, anti endomisio	Donna	Sangue

MULLERIAN ANOMALIES

3D ULTRASOUND / HYSTEROSCOPY

URSASCREEN®
Unexplainde Recurrent
Spontaneous Abortion
Screening

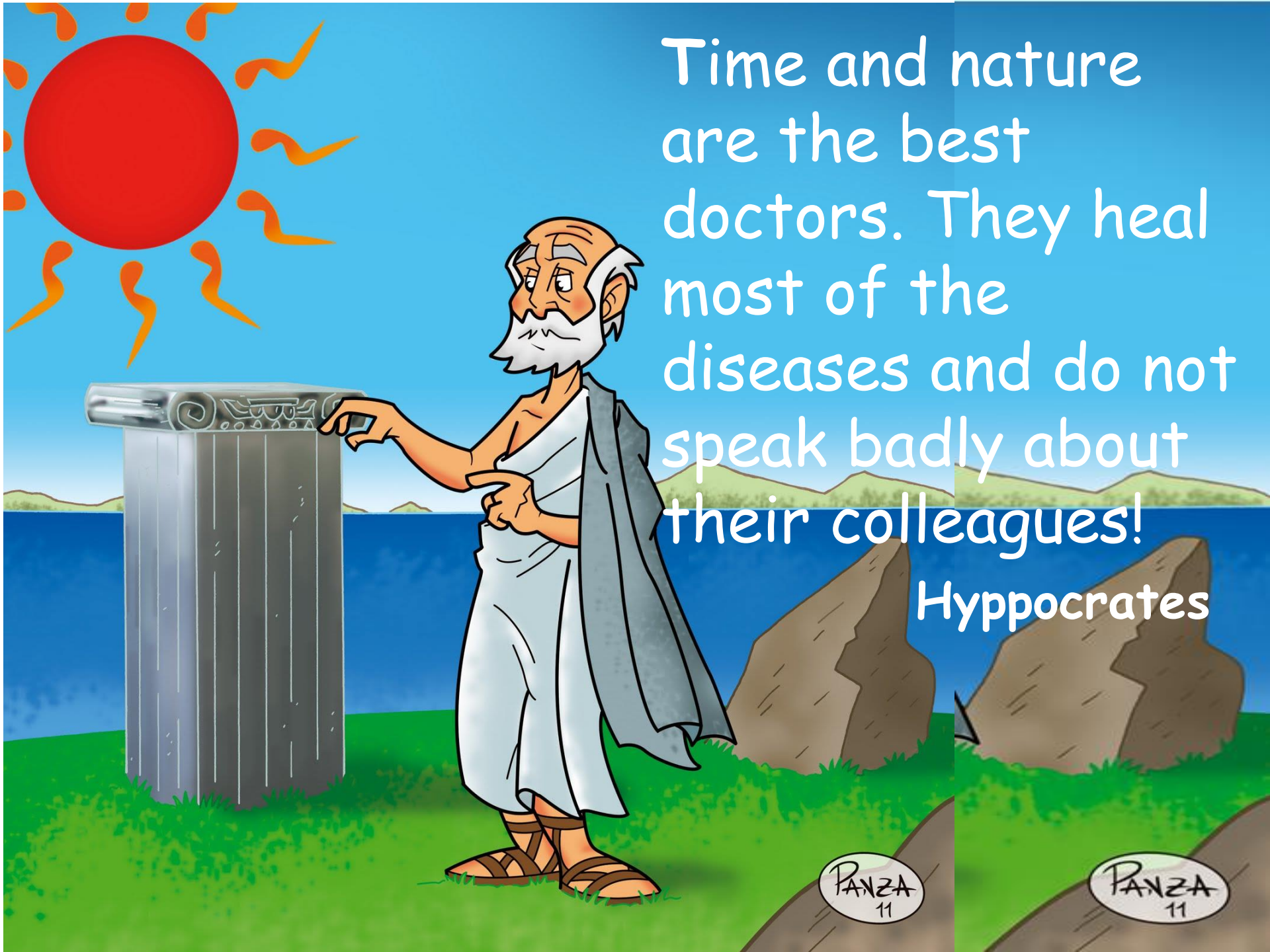
URSASCREEN® *Plus*
Unexplained Recurrent
Spontaneous Abortion
Screening *Plus*

RICERCHE	UOMO/DONNA O ENTRAMBI	MATERIALE BIOLOGICO
SCREENING GENETICI **Analisi bioinformatica completa dell'Esoma mediante NGS per la ricerca di mutazioni specifiche che sono riportate in letteratura come responsabili di poliabortività:** **- Analisi delle regioni: 22q11.23/GSTT1, 3p22.2/CTDSPL, 6p21.32/HLA, 8p22 MSR1, 14q32.33/AKT1 (mediante esame del cariotipo molecolare genomico)** **- Analisi mutazioni gene NALP7, gene SYCP3, gene WNT6, gene CEP250, gene CGB, gene NLRP10, gene PROKR1, gene FOXP3, gene OSBPL5, gene HLA-E (mediante Next Generation Sequencing o NGS)** **- Analisi gene HLA-G (con metodica complementare)** *Tutte le informazioni verranno analizzate mediante specifico programma bioinformatico: Altamedica URSASCREEN™*	**Donna**	**Sangue in EDTA o tampone buccale**

Let’s GO BACK in THE TIMES…. AGAIN!

We reflect.
if hundreds of generations believed that drinking the water of the Nile ,with the dust of the temple of Phile, preserves pregnancies, it means that even the sandstone of the temple worked … or not!

May be this worked as it looked like they worked our therapies in the past decades!


Time and nature are the best doctors. They heal most of the diseases and do not speak badly about their colleagues!
Hyppocrates
PANZA 11
PANZA 11