Convegno Microangiopatie Trombotiche

Roma, 19 Febbraio 2016

UNIVERSITÀ CATTOLICA del Sacro Cuore

Problematiche di tipo ostetrico

A. Lanzone, S. Salvi

In Pronto Soccorso

A 23 settimane di gestazione

Emocromo :

- Hb 8 g/dl , MCV 99 fl
- GB 15.140/mmc,
- PLT 19.000/mmc

Schistociti : 2%
Reticolociti: 6.8%, 156 x 109/l

Chimica:

- Creatinina 1,1 mg/dl
- LDH 2642 UI/l
- Bilirubina tot 2,7 mg/dl
- Bilirubina diretta 0,6 mg/dl
- GOT 92 UI/l, GPT 113 UI/l,

Piastrinopenia in Gravidanza

Pregnancy-specific	Not pregnancy-specific
Gestational thrombocytopenia	Primary immune thrombocytopenia
Preeclampsia/Eclampsia	Secondary immune thrombocytopenia
HELLP syndrome	Viral infection (HIV, Hep C, CMV, EBV, ot hers)
Acute fatty liver	Autoimmune disorders (SLE, others)
	Antiphospholipid antibodies
	Thrombotic microangiopathies
	*Thrombotic thrombocytopenic purpura**
	*Hemolytic-uremic syndrome**
	Disseminated intravascular coagulation (DIC)
	Bone marrow (MDS, myelofibrosis)
	Nutritional deficiencies
	Drugs
	*Type IIB vWD induced thrombocytopenia**
	Inherited thrombocytopenia (May-Hegglin, etc)
	Hypersplenism

McCrae KR Hematology 2010

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McCrae KR Hematology 2010

Imitators of Severe Pre-eclampsia

Baha M. Sibai, MD

2009

Table 1 Imitators of Severe Pre-eclampsia/HELLP Syndrome

- AFLP
- TTP
- HUS
- Exacerbation of lupus erythematosus
- Catastrophic antiphospholipid syndrome
- Systemic viral sepsis (disseminated herpes)
- Systemic inflammatory response syndrome/septic shock
- Other conditions (cholestasis of pregnancy, necrotizing pancreatitis, etc.)

TPP in obstetrics

- 1/25000 deliveries
- 1/2000 deliveries in High Risk Pregnancy Unit
- 1/20 deliveries among piastrinopenic patients

- Pregnancy was the initial and often the only precipitant of TTP

Maternal/Perinatal outcome in TPP/HUS

- Maternal

  death 17%

  CNS injury 3%

  Renal injury 18%

- Fetal losses 45%

Women 71; pregnancies 81

Sibai et al, 2009

Imitators of Severe Pre-eclampsia

Baha M. Sibai, MD

2009

"I disordini microangiopatici della gravidanza costituiscono per il clinico una **sfida diagnostica difficile se non impossibile**"

"**L'elevata similitudine dei quadri clinici e dei reperti laboratoristici,** rende una diagnosi differenziale quasi impossibile anche per il clinico più esperto"

Epoca d'esordio e Diagnosi Differenziale

Feature	Preeclampsia	HELLP	AFLP	aHUS	TTP	CAPS	SLE
Hypertension	+++	+++	+	++	+	+/–	++
Proteinuria	+++	++	+/–	+++	+/–	+	+++
Nausea/vomiting	+	+	++	+/–	+/–	+/–	+/–
Abdominal pain	+/–	++	++	+/–	+/–	+/–	+/–
Jaundice	+/–	+/–	++	+/–	+/–	+/–	+/–
Neurologic symptoms	+	+	+	+/–	++	++	+
Thrombocytopenia	+	+++	+	+++	+++	+	+
Hemolysis	+/–	+++	+	+++	+++	+/–	+
Raised bilirubin	+/–	+++	+++	+++	+++	+/–	+/–
Renal impairment	+/–	+	++	+++	+	++	++
DIC	+/–	++	+++	+/–	+/–	+/–	+/–
Hypoglycemia	+/–	+/–	+++	+/–	+/–	+/–	+/–
Elevated ammonia	+/–	+/–	+	+/–	+/–	+/–	+/–
Elevated transaminases	+	+++	+++	+/–	+/–	+/–	+
Epoca d'esordio	II/III	II/III		Postpartum	I/II	Qualsiasi Epoca	

McCrae KR Hematology 2010

The ***first and most crucial problem*** is differentiating HELLP syndrome from TTP/HUS

Modified from Pourrat O et al. (2015)

The mainstay of treatment of preeclampsia-eclampsia and HELLP Syndrome is delivery of the fetus

Lindheimer MD et al. (2010)

Delivery does not generally cause resolution of TTP and it is not routinely indicated

Gernsheimer T et al. (2012)

Diagnosi differenziale

- Importanza della **diagnosi differenziale** in gravidanza è critica al fine di poter correttamente impostare la migliore strategia terapeutica

Diagnosi Differenziale

Table IV. Typical features in pregnancy-associated microangiopathies.

	MAHA	Thrombo cytopenia	Coagulo pathy	HBP	Abdominal symptoms	Renal Impairment	Neurological symptoms
PET	+	+	±	+++	+	±	++
HELLP	+	++	±	+	+++	+	±
TTP	++	+++	–	±	+	++	+++
HUS	+	++	±	++	+	+++	±
AFLP	±	+	++++	+	+++	++	+
SLE	+	+	±	+	±	++	+
APLS	+	++	±	±	±	±	±

PET, pre-eclampsia; HELLP, haemolysis, elevated liver enzymes and low platelets; TTP, thrombotic thrombocytopenia purpura; HUS, haemolytic-uraemic syndrome; AFLP: acute fatty liver of pregnancy; SLE, systemic lupus erythematosus; APLS, Antiphospholipid syndrome (catastrophic), MAHA, microangiopathic haemolytic anaemia; HBP, hypertension.

Scully British Journal of Haematology 2012

Diagnosi Differenziale

Laboratory Findings	HELLP Syndrome	AFLP	TTP	HUS	Exacerbation of SLE
Thrombocytopenia (<100,000/mm^3)	>20,000	>50,000	≤20,000	>20,000	>20,000
Hemolysis	50-100%	15-20%	100%	100%	14-23% w/APA*
Anemia	<50%	Absent	100%	100%	14-23% w/APA
DIC	<20%	73%	Rare	Rare	Rare
Hypoglycemia	Absent	61%	Absent	Absent	Absent
VW factor multimers	Absent	Absent	80-90%	80%	<10%
ADAMTS 13% < 5%	Absent	Absent	33-100%	Rare	Rare
Impaired renal function	50%	90-100%	30%	100%	40-80%
LDH (IU/L)	≥600	Variable	>1000	>1000	with APA
Elevated ammonia	Rare	50%	Absent	Absent	Absent
Elevated bilirubin	50-60%	100%	100%		<10%
Elevated transaminases	100%	100%	Usually mild†	Usually mild†	with APA

Sibai BM Seminars in Perinatology 2009

Diagnosi differenziale

Dinanzi ad un quadro clinico suggestivo di HELLP ad insorgenza precoce o in presenza di una severa piastrinopenia, il dosaggio di ADAMTS-13 andrebbe sempre eseguito (Delmas et al BMC Pregnancy and Childbirth 2015)

In **urgenza** il dosaggio di ADAMTS-13 non può essere effettuato..

Diagnosi differenziale

Laboratory findings	AFLP	HELLP	TTP
Transaminitis (AST/ALT elevation)	+++	++	-/+
Hemolytic anemia	+/-	+/++	++/+++
Thrombocytopenia	+	++	++/+++
Antithrombin deficiency	+++	++	-
DIC	Common	Variable	Absent
Hypoglycemia	Common	Absent	Absent
Renal insufficiency	20%-100%	3%-15%	30%-80%

Sibai BM Seminars in Perinatology 2009

The Journal of Maternal-Fetal & Neonatal Medicine
2012

A high LDH to AST ratio helps to differentiate pregnancy-associated thrombotic thrombocytopenic purpura (TTP) from HELLP syndrome

Objective: Differentiating between pre-eclampsia/HELLP syndrome and pregnancy-associated thrombotic thrombocytopenic purpura (TTP) is difficult but important in order to undertake timely and potentially life-saving plasma exchange (PEX) therapy for TTP recovery. We review our institutional experience with pregnancy-associated TTP and determine if the ratio of LDH to AST reliably distinguishes patients with TTP from those with HELLP syndrome.
Study design: This is a **retrospective case control study** of all pregnant/puerperal patients with TTP from a single tertiary care center during 1986–2006. Laboratory findings in patients with **TTP** were compared to patients who met all criteria for **class 1 or 2 HELLP syndrome** within the first 24 hours of hospital admission during 2000–2007.

The Journal of Maternal-Fetal & Neonatal Medicine
2012

A high LDH to AST ratio helps to differentiate pregnancy-associated thrombotic thrombocytopenic purpura (TTP) from HELLP syndrome

Results: Thirteen pregnant (*n* = 10) or puerperal (*n* = 3) patients with TTP were identified; 11 cases were primary, 2 were recurrent. TTP laboratory findings included LDH to AST ratios of 77 ± 42.17; Patients with HELLP syndrome (*N* = 83) had significantly lower LDH to AST ratios of 20.04 ± 2.13. Based on an ROC analysis, an LDH/AST ratio ≥22.12 discriminates well between TTP and antenatal HELLP subjects (AUC = 0.99). *Conclusion*: **A high LDH to AST ratio >22.12 suggests that TTP is a more likely diagnosis than HELLP syndrome in the third trimester pregnant patient, presenting with findings that could be compatible with either diagnosis**. In these circumstances, it is advisable to obtain hematology consultation and to consider PEX implementation.

Diagnosi differenziale

- Per **l'HELLP Syndrome** il Parto costituisce tutt'oggi l'unica strategia terapeutica definitivamente efficace..
- ..la **TTP** così come **l'APS catastrofica e il LES flare** non richiedono necessariamente il Parto ma possono avvalersi di trattamenti terapeutici specifici anche in gravidanza

- Il management ostetrico e la strategia terapeutica si differenziano in maniera essenziale sulla base dell'**epoca di esordio**

Management **TTP**

- L'iniziale management della TTP **in gravidanza** non differisce da quello di pazienti **non in gravidanza**
- L'espletamento del parto usualmente non causa la risoluzione della TTP e **non è indicato di routine**
- La ***Plasma exchange*** è la sola efficace terapia e deve essere intrapresa quanto prima
- Il parto si raccomanda per le sole donne che non rispondano alla *Plasma exchange* (Diagnosi sicura?)

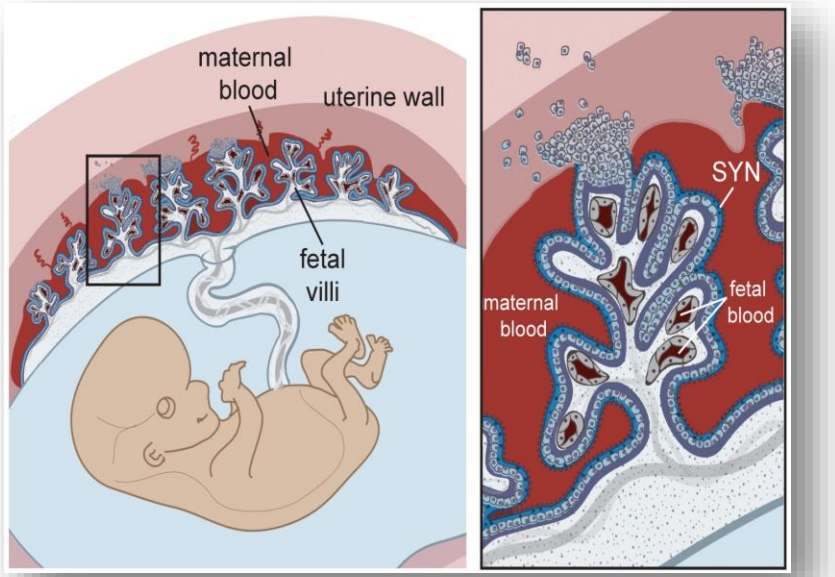
Gernsheimer et al. Blood 2013

Management **TTP**

- L'importanza del trattamento è **materno - fetale**

- La microangiopatia trombotica che si manifesta in modo sistemico nella TTP coinvolge infatti anche le arterie deciduali in gravidanza (Wurzei JM NEJM 1979)

- **Aumento del rischio** di Preeclampsia associata, Iposviluppo fetale, Morte endouterina



Gasparri et al. Hemapheresis 2015

Incidence of obstetrical thrombotic thrombocytopenic purpura in a retrospective study within thrombocytopenic pregnant women. A difficult diagnosis and a treatable disease

Yahsou Delmas[1,2*], Sébastien Helou[1,6], Pierre Chabanier[2,3], Anne Ryman[2,4], Fanny Pelluard[5,6], Dominique Carles[5,6], Pierre Boisseau[7], Agnès Veyradier[8,9], Jacques Horovitz[3,6], Paul Coppo[9,10,11] and Christian Combe[1,2,6]

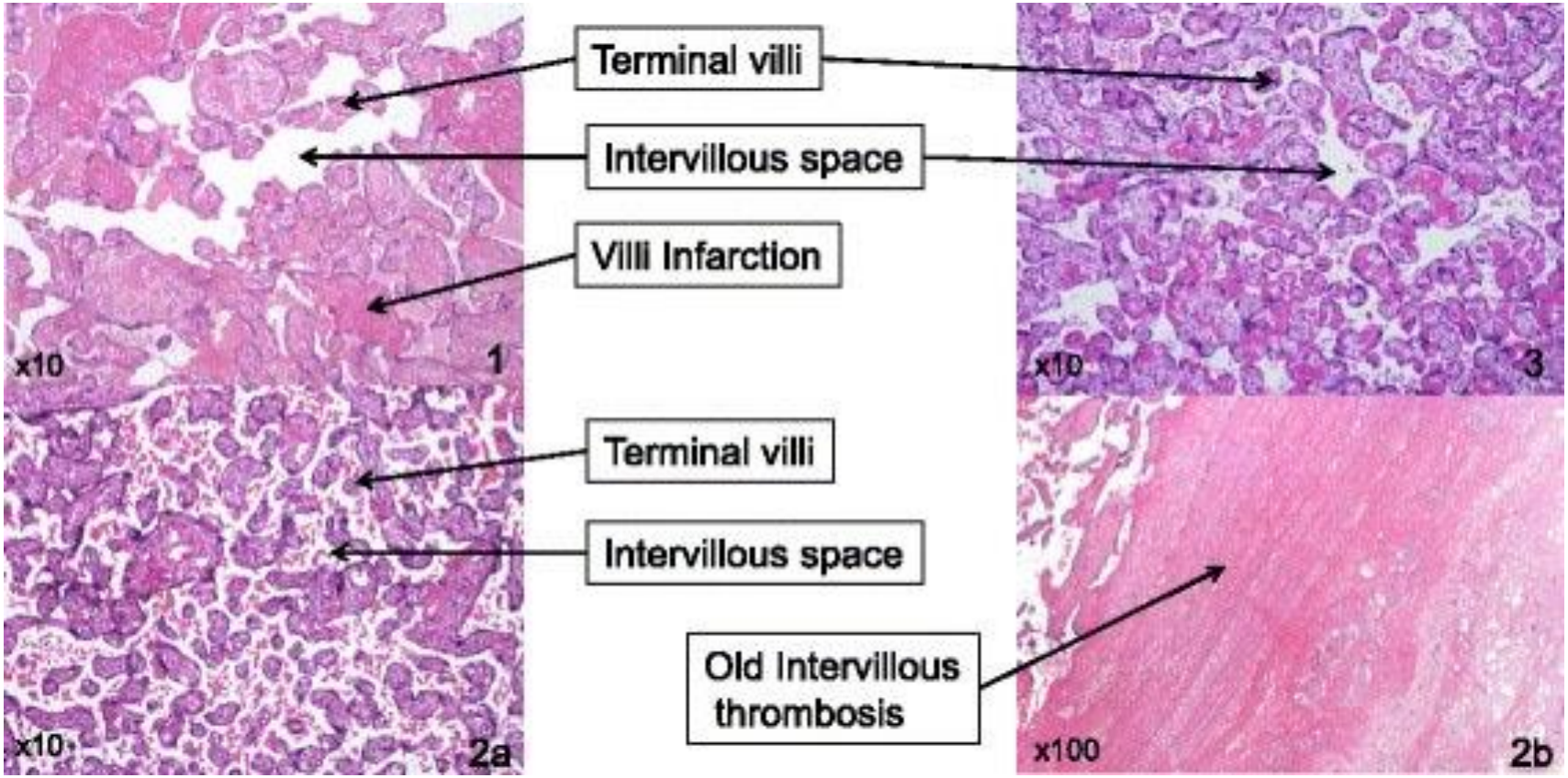
Methods: A monocentric retrospective study (2008–2009) was conducted among pregnant women followed in a tertiary care obstetrical unit who experienced at least one episode of severe thrombocytopenia (platelets ≤75 G/L) during 2008 and 2009. In cases of uncertain aetiology of thrombocytopenia, ADAMTS-13 activity was assessed by the full length technique.

BMC Pregnancy & Childbirth

2015

Analisi isto-patologica dei tessuti placentari della Paziente B nelle tre diverse gravidanze

1. I Gravidanza NON trattata (TTP a 33 settimane con **Morte Neonatale**)
2. II Gravidanza trattata da 13 settimane (**Buon outcome**, Parto a 35 settimane)
3. III Gravidanza trattata da 4 settimane (**Ottimale outcome**, Parto a 38 settimane)



Delmas et al. BMC Pregnancy and Childbirth (2015)

CLINICAL TRIALS AND OBSERVATIONS

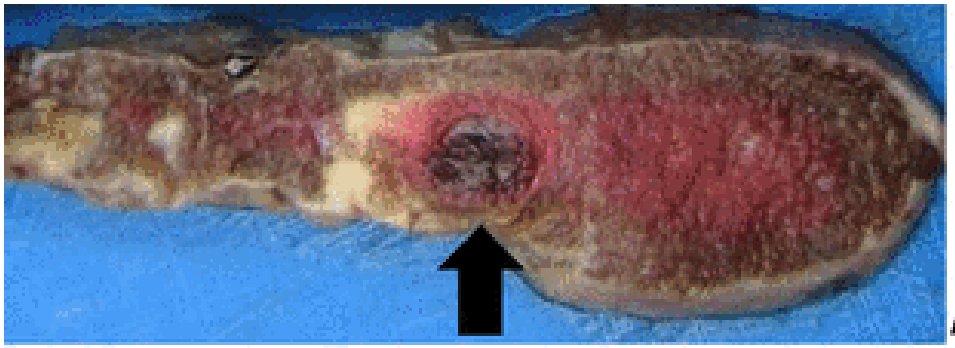
Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes

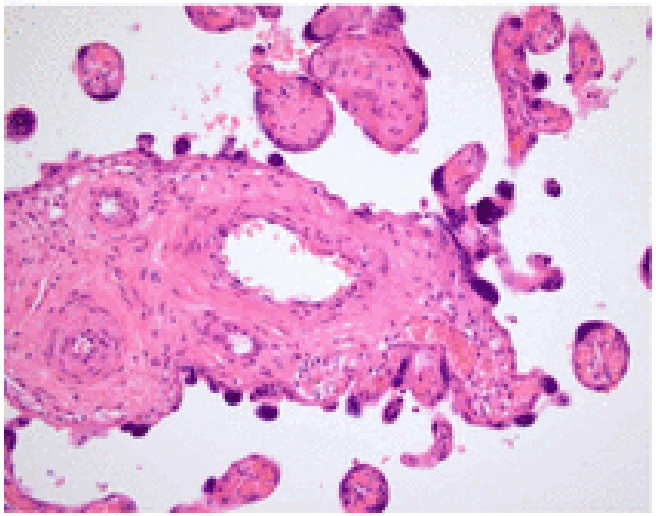
Marie Scully,[1] Mari Thomas,[2] Mary Underwood,[2] Henry Watson,[3] Katherine Langley,[2] Raymond S. Camilleri,[4] Amanda Clark,[5] Desmond Creagh,[6] Rachel Rayment,[7] Vickie Mcdonald,[8] Ashok Roy,[9] Gillian Evans,[10] Siobhan McGuckin,[1] Fionnuala Ni Ainle,[11] Rhona Maclean,[12] William Lester,[13] Michael Nash,[14] Rosemary Scott,[1] Patrick O Brien,[1] and collaborators of the UK TTP Registry

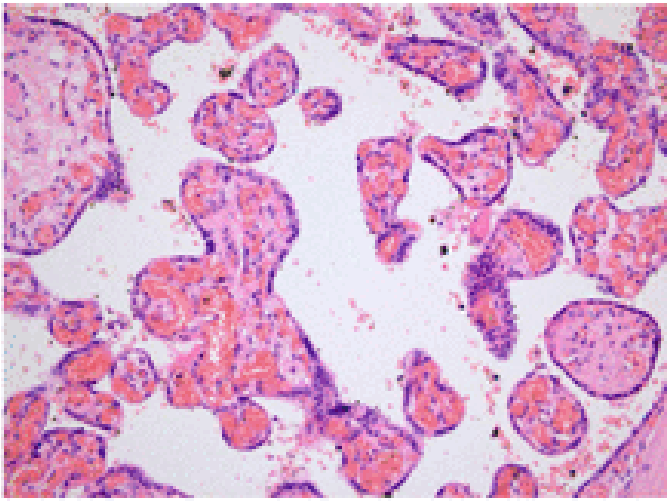
BLOOD, 10 JULY 2014 · VOLUME 124, NUMBER 2

Analisi dei tessuti placentari in una donna con TTP acquisita in gravidanza e nella gravidanza successiva trattata con Plasmaferesi

A. Placenta di gravidanza con TTP non trattata con parto prematuro a 28 settimane
B. Esame istologico della placenta con TTP non trattata con parto prematuro a 28 settimane
C. Gravidanza successiva trattata con parto a 36 settimane


A


B

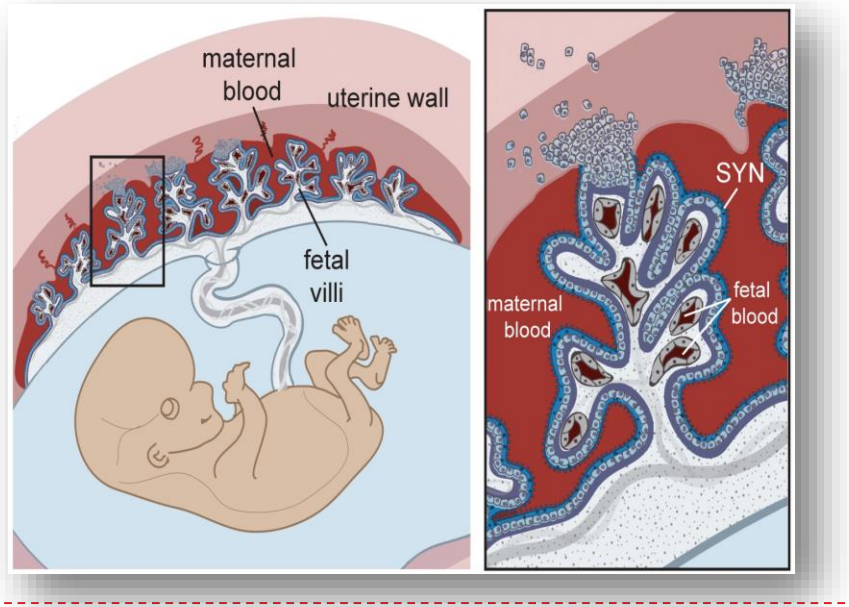

C

Scully M et al. Blood (2014)

Management **TTP**

- La maggioranza dei casi si sviluppano antepartum ad un'epoca gestazionale media di **26 settimane**

- Pertanto il parto prematuro e la prematurità costituiscono tra i **principali rischi feto- neonatali**



Sibai BM et al. Seminars in Perinatology 2009

TPP- Maternal-fetal outcome and theraphy

cTTP

Fetal survival : 58% ; after PEX 100%; maternal death 0%

aTTP

Fetal survival : 65% ; after PEX 75%; maternal death 0%

Late onset 46% (66% for cTTP)

20-30wks 38%

< 20 wks 15%

Scully et al. , *Blood* 2014

Management **TTP**

- In caso di **TTP congenita** il rischio di recidiva nella successiva gravidanza è del 100%, in assenza di una profilassi con *plasma exchange* che deve essere intrapresa quanto prima (Veyradier A et al. Hereditary Genetics 2012)

- In caso di **TTP acquisita** il rischio di recidiva nella successiva gravidanza è del 20% circa (Veyradier A et al. Hereditary Genetics 2012)

In quest'ultimo caso si suggerisce di utilizzare il dosaggio seriato di ADAMTS-13 per identificare quelle donne a più alto rischio di recidiva e sulle quali iniziare la Plasma exchange

(Scully M Br J Hematol 2012, Gernsheimer et al. Blood 2013)

Pregnancy complications in acquired thrombotic thrombocytopenic purpura: a case control study

Barbara Ferrari[1], Alberto Maino[1], Luca A Lotta[1], Andrea Artoni[1], Silvia Pontiggia[1], Silvia M Trisolini[2], Alessandra Malato[3], Frits R Rosendaal[1,4,5] and Flora Peyvandi[1,6*]

Ferrari *et al. Orphanet Journal of Rare Diseases* 2014, **9**:193

Methods

We conducted a nested case control study of women who became pregnant after the diagnosis of acquired TTP. Among them, we contrasted data of women who experienced a complicated pregnancy (i.e., cases of either gravidic TTP or miscarriage) to those with an uncomplicated pregnancy (i.e., controls).

Pregnancy complications in acquired thrombotic thrombocytopenic purpura: a case control study

Ferrari *et al. Orphanet Journal of Rare Diseases* 2014, **9**:193

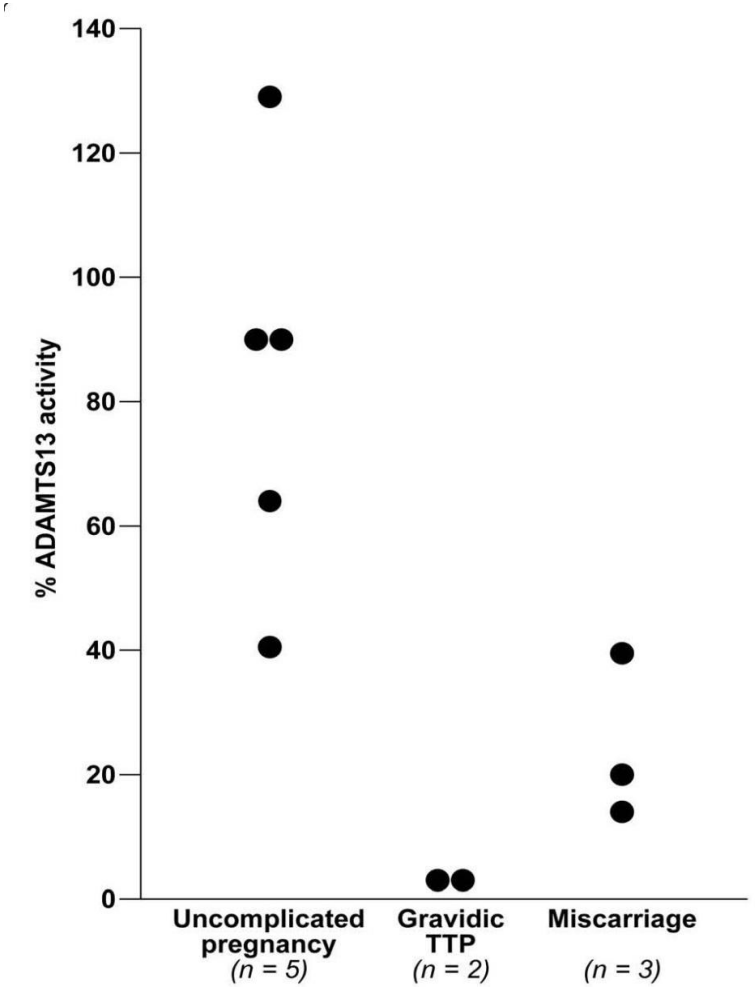


Figure 2 ADAMTS13 activity levels in the first trimester

Pregnancy complications in acquired thrombotic thrombocytopenic purpura: a case control study

Ferrari *et al. Orphanet Journal of Rare Diseases* 2014, **9**:193

Table 4 Risk estimates for gravidic TTP associated with demographic and clinical variables

	Gravidic TTP (n = 4)	Uncomplicated pregnancy (n = 6)	OR (95% CI)
Age ≤ 30 years	3	2	6.0 (0.4 101.6)
Age >30 years	1	4	ref
Primigravidae	2	5	0.2 (0.01 3.7)
Multigravidae	2	1	ref
Non-recurrent TTP	3	2	6.0 (0.4 101.6)
Recurrent TTP	1	4	ref
Time from previous TTP ≤24 months	1	1	1.7 (0.08 37.7)
Time from previous TTP >24 months	3	5	ref
ADAMTS13 activity <25% in the first trimester*	2	0	∞ (2.9 - ∞)
ADAMTS13 activity ≥25% in the first trimester*	0	5	ref
Positive anti-ADAMTS13 antibodies in any trimester	4	0	∞ (6.6 - ∞)
Negative anti-ADAMTS13 antibodies in any trimester	0	6	ref

*ADAMTS13 activity levels in the first trimester were available in 2 cases and 5 controls.

Pregnancy complications in acquired thrombotic thrombocytopenic purpura: a case control study

Ferrari *et al. Orphanet Journal of Rare Diseases* 2014, **9**:193

Table 5 Risk estimates for miscarriage associated with demographic and clinical variables

	Miscarriage (n = 5)	Uncomplicated pregnancy (n = 6)	OR (95% CI)
Age ≤ 30 years	1	2	0.5 (0.03 8.06)
Age >30 years	4	4	ref
Primigravidae	2	5	0.1 (0.01 2.2)
Multigravidae	3	1	ref
Non-recurrent TTP	4	2	8.0 (0.5 127.9)
Recurrent TTP	1	4	ref
Time from previous TTP ≤24 months	4	1	20.0 (0.9 429.9)
Time from previous TTP >24 months	1	5	ref
ADAMTS13 activity <25% in the first trimester*	2	0	∞ (1.2 - ∞)
ADAMTS13 activity ≥25% in the first trimester*	1	5	ref
Positive anti-ADAMTS13 antibodies in the first trimester*	3	0	∞ (4.1 - ∞)
Negative anti-ADAMTS13 antibodies in the first trimester*	0	5	ref

*ADAMTS13 activity levels and anti-ADAMTS13 antibodies in the first trimester were available in 3 cases and 5 controls.

HUS in gravidanza

- Il plasma exchange è di peculiare importanze nella aHUS anche in gravidanza

- Il suo ruolo è di risolvere rapidamente l'emolisi e prevenire danni irreversibili al rene

Mussoni MP et al 2014

HUS in gravidanza

Case Report

Innovative therapeutic approach: Sequential treatment with plasma exchange and eculizumab in a pregnant woman affected by atypical hemolytic-uremic syndrome

Maria Pia Mussoni [a,*], F.A. Veneziano [a], L. Boetti [a], C. Tassi [a], C. Calisesi [a], S. Nucci [a], A. Rigotti [b], I. Panzini [c], G. Ardissino [d]

Transfusion and Apheresis Science 51 (2014) 134–136

- Al fine di evitare un eccessivo prolungamento dell'uso della **plasma exchange (PEX)** in gravidanza, sostituita la PEX con Eculizumab

Eculizumab

- Anticorpo monoclonale anti-C5
- Off-label in gravidanza
- Approvato nel trattamento dell'emoglobinuria parossistica notturna
- Dal 2009 usato anche nel trattamento della aHUS, ma **NON in gravidanza**

Köse O, Zimmerhackl LB, Jungraithmayr T, Mache C, Nürnberger J. *New treatment options for atypical hemolytic uremic syndrome with the complement inhibitor* ***eculizumab***. Semin Thromb Hemost. 2010 Sep;36(6):669-72.

Nürnberger J, Philipp T, Witzke O, Opazo Saez A, Vester U, Baba HA, Kribben A, Zimmerhackl LB, Janecke AR, Nagel M, Kirschfink M.
Eculizumab *for atypical hemolytic uremic syndrome.* N Engl J Med. 2009 Jan

Case report

Eculizumab for the treatment of preeclampsia/HELLP syndrome

R.M. Burwick [1], B.B. Feinberg*

combined lung and kidney transplantation. Transplantation. 2013 Oct 27;96(8):e58-9.

Placenta, 2013

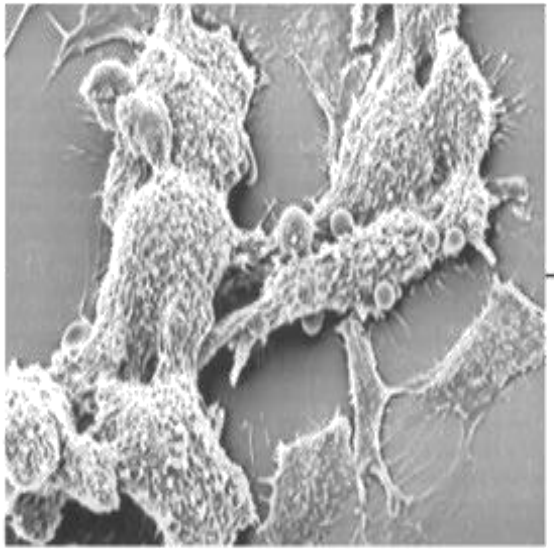
Cañigral C, Moscardó F, Castro C, Pajares A, Lancharro A, Solves P, de la Rubia J, Carpio N, Sanz MA. ***Eculizumab*** *for the treatment of pregnancy-related atypical hemolytic uremic syndrome.* Ann Hematol. 2013 Dec 5.

Attivazione del complemento: link patogenetico unico nella HUS e TTP

HELLP?

Disease	Cause	Effect
STEC-HUS	Stx	P-selectin expression
aHUS	Gene mutation Anti-CFH antibodies	Defective complement regulation
TTP	ADAMTS13 deficits	UL-VWF multimers

Complement activation



Microthrombi

L'iperattivazione del complemento sia essa causata degli effetti di tossine batteriche, da difetti genetici nel sistema del complemento o da trombi piastrinici derivanti da carenza di ADAMTS13, culmina in una microangiopatia trombotica

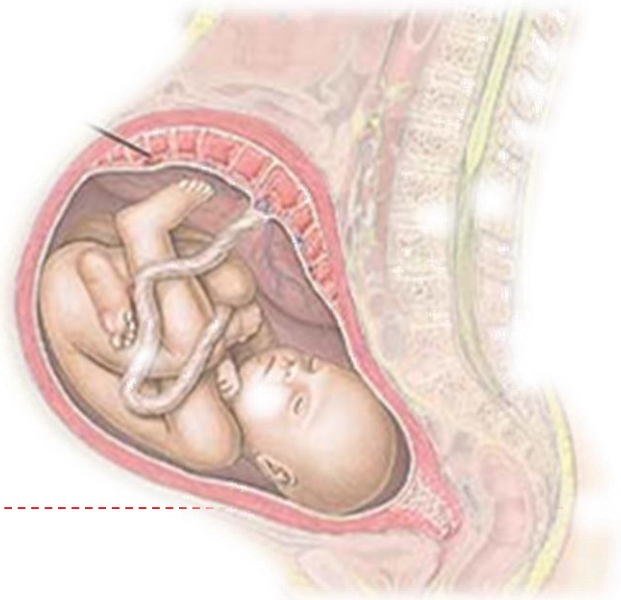
Noris M. et al. 2012

Complemento nella gravidanza fisiologica

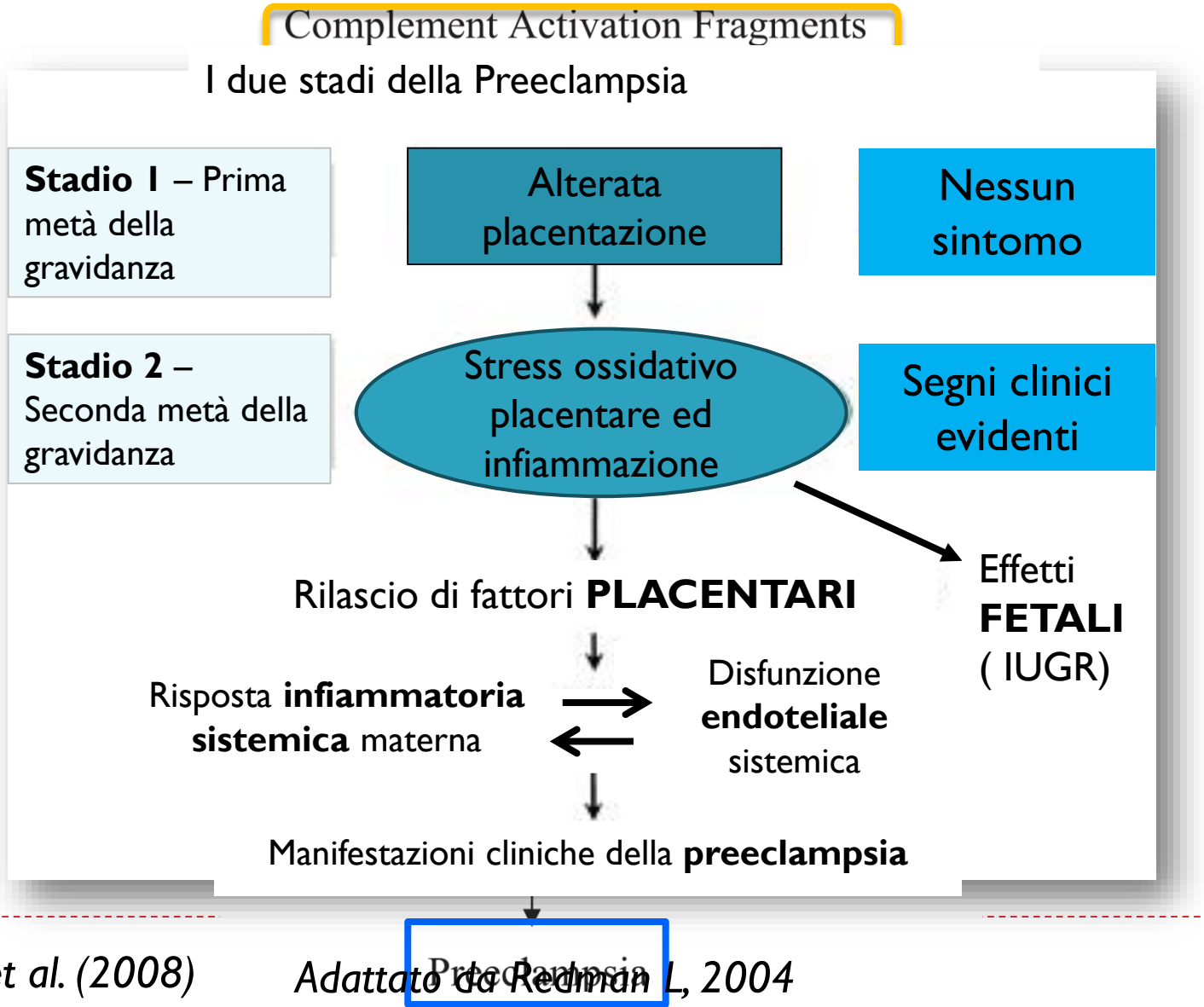
✓ La placenta costituisce un importante sito di azione del complemento, che protegge l'interfaccia materno fetale da patogeni esterni e promuove la rimozione di cellule apoptotiche e complessi immuni

- Il **C1q** svolge un importante ruolo nel promuovere l'invasione del trofoblasto nella parete uterina materna (Agostinis C, et al 2010)

- Il **C3** si è dimostrato assicurare l'evolutività della gravidanza nelle fasi precoci dell'impianto (Chow WN et al. 2009)



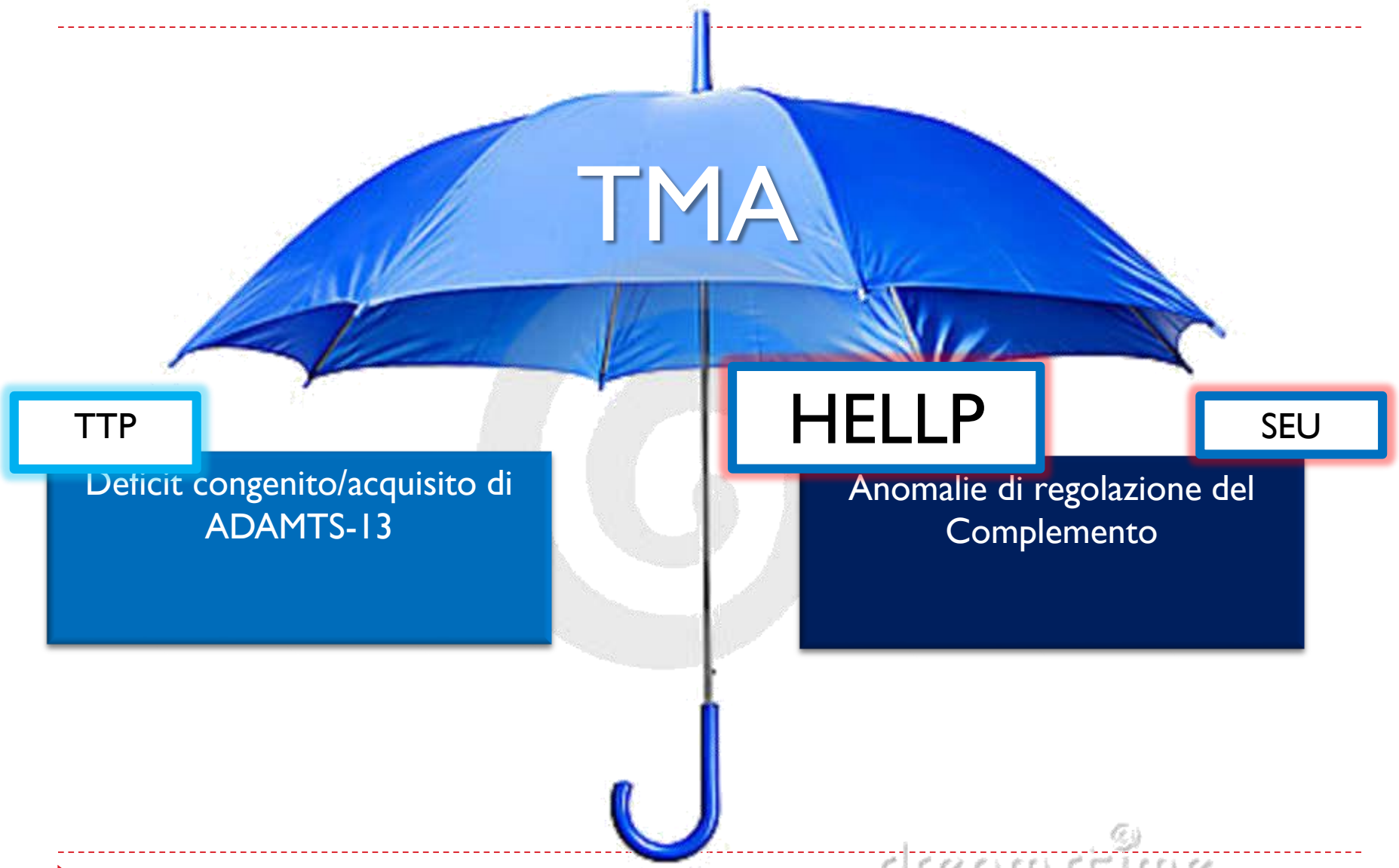
Complemento nelle patogenesi della Preeclampsia/HELLP



Lynch AM, et al. (2008)

Adattato da Redman L, 2004

Le Microangiopatie Trombotiche (TMA)



Fakhouri , F et al. (2008)

Conclusions

- The outcome of pregnancy in women presenting with either congenital or acquired TTP is closely related to the gestation at presentation;
- Pregnancy loss typically occurred in the second trimester for both groups;
- Prompt diagnosis and treatment before 20 weeks was surprisingly associated with positive pregnancy outcomes.