Avancées scientifiques du XXIème Congrès de l'ISTH à l'interface Hémostase/Gynécologie/Obstétrique

P. de Moerloose

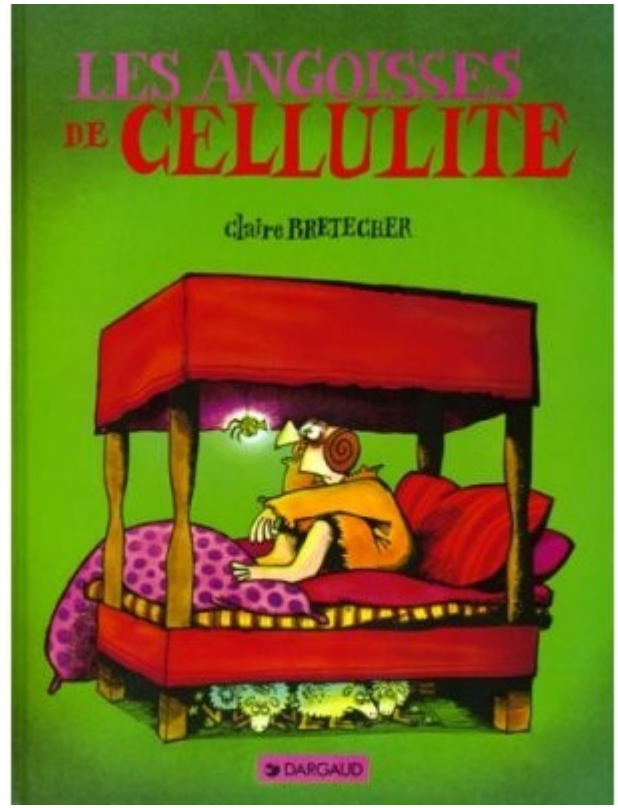
HUG
POST TENEBRAS LUX
Hôpitaux Universitaires de Genève

Réflexions….

Mais qu’est-ce

je vais bien

leur raconter?



Réconfort…

En ce qui concerne le fond de votre intervention, nous avions effectivement parlé des Highlights de l'ISTH 2007 en choisissant préférentiellement des thèmes qui ne sont pas traités, comme par exemple l'impact des marqueurs de la thrombophilie génétique dans la pathologie vasculaire placentaire, mais bien sûr il s'agit d'un thème parmi d'autres et votre conférence, la plus longue de toutes, devrait permettre d'exprimer votre opinion sur d'autres sujets que vous choisiriez.

Avec toutes mes amitiés

Philippe

Selection: « hormones, pregnancy, women issues »

- 1 State of the Art
- 11 communications orales
- 80 posters
- Quelques autres communications

- Out : tous les exposés « bleeding »

Presentation

- Thrombophilic markers and pregnancy outcome
- Treatments (LMWH, fondaparinux, ..)

Est-ce que des examens d’hémostase permettent de prédire le succès d’une grossesse?

Plasma coagulation tests and genetic thrombophilic studies are mandatory for preventing recurrent abortions or repeated fetal loss in healthy women

Etude de 43 femmes, tests de thrombophilie « classique », fibrinolyse, aPL divers, homocystéine

39 ont une « anomalie », pas de contrôles

Conclusion : faire un ”well-reasoned screening must be considered in women with RA or RFL”

R. Musso, F. Nardo, H, D. Cultrera, G. Sortino, M. Arraro, A. Cipolla, E. Di Francesco, M. Musso, A. Musso. Catania

Placenta-mediated pregnancy complications

- 1st, 2nd, 3rd trimester
- Early fetal loss, late fetal loss
- Abortion, miscarriage, placental abruption
- Preeclampsia (moderate, severe), eclampsia
- Late pregnancy outcome (growth restriction, premature delivery, intrauterine fetal death, …)
- ……

Inherited thrombophilia and preeclampsia in a cohort of 5337 women: results of the Montreal PE study (OC)

We performed a multicenter case control study nested within a large, prospectively recruited cohort.

Methods: 5337 pregnant women at 4 Montreal hospitals were recruited. At 24-26 weeks gestation, women were interviewed, had blood samples frozen and were followed to delivery. We prospectively identified women who developed PE (113 cases) and chose as controls 458 women who delivered and did not have PE or non-proteinuric gestational hypertension. Cases and controls provided placentae for pathological evaluation.

S. Kahn, R. Platt, H. McNamara, M. Kramer, Montreal

Inherited thrombophilia and preeclampsia within a cohort of 5337 women: results of the Montreal PE study

Results: FV Leiden, IIG20210A or MTHFR677 were present in 14% of cases and 21% of controls. Regression analyses adjusted for age and PE risk factors showed lack of association between PE and thrombophilia (OR 0.97) and no detectable interactions between thrombophilia and diabetes, hypertension, BMI or primigravidity. Microscopic findings of placental underperfusion were noted in 63% of cases vs. 46% controls ($p<0.001$) but were not associated with thrombophilia.

Conclusions: We did not find an association between inherited thrombophilia and PE. Placental underperfusion is associated with PE, but this does not appear to be consequent to thrombophilia

FVL and PGV associated with placenta mediated pregnancy complications: a large prospective cohort study (OC)

We sought to determine if the FVL and prothrombin gene variant (PGV) were associated with a composite of the placenta mediated pregnancy complications.

Methods: Prospective cohort study of pregnant women <16 weeks gestational age. Participants had blood drawn at the time of inclusion and were followed to the time of delivery with pregnancy. Variables = composite outcome of pregnancy loss, IUGR <10th percentile, pre-eclampsia or placental abruption and FVL and/or PGV. Sample size estimate of 3000 to have > 80% power to detect and OR of 1.6 or greater with a priori assumed event rate of 17%.

M. Rodger, M. Walker, S. Wu Wen, G. Smith, N. Carson, B. Gin, P. Wells. Ottawa

FVL and II gene variant associated with placenta mediated pregnancy complications: a large prospective cohort study

Results: Of 5490 selected, 3130 eligible women consented to participate and 3006 had FVL and PGV genotyping and 2942 had complete primary outcome data. Mean age was 31 yrs with a mean 2.2 prior pregnancies. 6.4% had FVL or PGV.

A composite primary outcome occurred in 296/2753 (10.8%) subjects with neither FVL nor PGV, 18/131 (13.7%) with FVL and 9/61 (14.8%) with PGV. FVL or PGV was associated with the placenta mediated pregnancy complication with an odds ratio of 1.38 (95% CI 0.90-2.12).

Conclusions: FVL and PGV may be only weakly associated with placenta mediated pregnancy complications

FVL, FIIG20210A and MTHFR T677T genotypes: relation with early recurrent pregnancy losses?

Evaluation of three mutations in women with first-trimester recurrent pregnancy losses and no thromboembolic history

Results. No difference between 212 cases and 181 controls

Conclusions. Molecular testing is not indicated for women with early recurrent pregnancy losses and negative thrombophilic history

A. Mougiou, M. Karakantza, G. Androutsopoulos, G. Decavalas, N. Zoumbos. Patras

Thrombophilia risk factors are associated with pregnancy related thromboembolism

Examinations of records of 328 women (733 pregnancies) who undergone thrombophilia screening because of pregnancy-associated complications; 97 (30%) had a thromboembolic event during pregnancy

Conclusions. Thrombophilia is most frequently found in conjunction with thromboembolism

A. Hvas, J. Ingerslev, JD. Salvig. Aarhus, DK

Blood group AB and FV Leiden as risk factors for pre-eclampsia (OC)

- PE complicates 3% of pregnancies. We assessed several inherited and acquired factors for the risk of pre-eclampsia, including FV Leiden and ABO blood group.

- **Methods:** This is a population-based nested case-control study of 100 000 consecutive pregnancies. Cases and controls were identified by combining national registers and according to strict criteria after checking all medical records. 248 cases with pre-eclampsia and 641 controls with uncomplicated pregnancy were studied.

L. Hiltunen, H. Laivuori, A. Rautanen, R. Kaaja, J. Kere, T. Krusius, M. Paunio, V. Rasi. Helsinki

Blood group AB and FV Leiden as risk factors for pre-eclampsia

Blood group AB in controls and subgroups of preeclampsia

	AB, n	OR
Controls, 641	39 (6.1%)	reference
PE, 248	32 (12.9%)	2.3 (1.4-3.7)
Severe PE, 168	23 (13.7%)	2.4 (1.4-4.2)
Early PE, 77	16 (20.8%)	4.0 (2.1-7.7)

Conclusions: Blood group AB was associated with increased risk for pre-eclampsia. FV Leiden was not a significant risk factor in this study population.

Est-ce que le FV Leiden ou certains groupes sanguins protègent les femmes de complications hémorragiques?

P-S-631. The Goal study: a prospective examination of the impact of FV Leiden and ABO blood groups on hemorrhagic and thrombotic pregnancy outcomes (4250 unselected pregnancies)

P-S-632. The influence of FV Leiden and ABO blood groups on hematology markers in early pregnancy (1252 unselected pregnancies)

P. Clark, I. Walker, L. Govan, I. Greer. Dundee, Glasgow

Conclusions

“We did not confirm the protective effect of FVL on pregnancy-related loss. We did not find an increased of many of the complications (VTE, PE, IUGR, pregnancy loss) which have been linked with FVL in retrospective studies, suggesting that there may be a limited utility in screening for the mutation in unselected subjects who present for pregnancy care”.

“We could find no association with either FVL or ABO group and early pregnancy hematology (iron deficiency)”

Si VL et II hétérozygotes ne sont pas ou à faible risque pour une complication obstétricale, peut-être que le fait d'avoir les deux mutations augmente le risque de faire une MTEV pendant la grossesse?

The risk of pregnancy-related VTE in double carriers of factor V Leiden and II G20210A (OC)

Introduction: The rate of VTE during pregnancy in double heterozygotes for factor VL and IIG20210A is not established. Thus, whether or not these women would benefit from antithrombotic prophylaxis with LMWH during pregnancy is still unknown.

Methods: The population was formed by women relatives of probands with VTE, who were pregnant at least once before diagnosis of thrombophilia. 52 double hh were compared to 104 single h for FVL and 104 single h for II G20210A. The rate of VTE events during pregnancy and puerperium was recorded.

T. Battaglioli, V. De Stefano, D. Tormene, L. Valdré, E. Grandone, A. Tosetto, I. Martinelli. A. Milan; Rome; Padua; Bologna; Foggia; Vicenza

The risk of pregnancy-related VTE in double carriers of factor V Leiden and II G20210A (OC)

Results: 155 pregnancies occurred in hh, 208 in h FVL and 216 in h of PT G20210A. All pregnancies occurred without antithrombotic prophylaxis.
No VTE events were recorded during pregnancy. VTE was observed in 2% of puerperia in double heterozygotes, 3% in single heterozygotes for FVL and 4% in single heterozygotes for PT G20210A (p = ns).

Conclusions: The risk of first VTE during pregnancy and puerperium in double heterozygotes for FVL and PT G20210A is not higher than that of single heterozygotes. As for single heterozygotes, antithrombotic prophylaxis during pregnancy does not appear to be justified in double heterozygotes.

The G20210A II variant and the risk of TE and fetal loss in pregnant women

Retrospective, multicentre, cohort study in women (354 pregnancies) belonging to families identified because of a symptomatic proband with isolated FII variant (355 controls, non carriers)

Conclusion. Female family members h FII variant do not seem to be at increased risk for fetal loss. One TE postpartum in the h FII group. Cost-benefit ratio studies of screening and thrombo-prophylaxis strongly needed.

D. Tormene, V. De Stefano, E. Grandone, A. T. Za, M. Margaglione, I. Martinelli. A. Tosetto, P. Castaman, P. Simioni. Padua; Foggia; Milan; Vicenza

Other markers?

Risk determinants of arterial thrombosis increase the risk of intrauterine growth restriction (OC)

We performed a case-control study to assess hereditary RF for arterial thrombosis in addition to venous thrombosis as risk determinants for IGR

Methods. 127 women with severe fetal IGR and 300 controls. Women with other reasons of IGR (history of venous thrombosis, fetal loss, and preeclampsia) were excluded. Fetuses were born alive after the 24th week of gestation.

A. Gerhardt, N. Howe, J. Kruessel, H. Bender, R. Scharf, R. Zotz. Dusseldorf

FR and intrauterine growth restriction

Results. Significant association with HPA-1b-1b (OR 3.1), increased fibrinogen (OR 2.8), vWF:Ag (OR 2.7), VIII:C (OR 1.7) lipoprotein a (OR 1.7). Combination of RF increases the risk, e.g. HPA-1b, Lp(a) and vWF: OR 14.0. No significant association with FVL or II G20210A.

Conclusions. Arterial risk factors are more important than venous risk factors for IGR. Important to examine whether subgroup of patients will benefit from specific antiplatelet agents.

Pregnancy morbidity is associated with low plasma TFPI, increased II generation and rAPC

Studies of 50 women with pregnancy complications, none had known heritable thrombophilia but 18 APA. Samples taken at least 6 weeks after the end of pregnancy. Normal ranges established in 20 normal women.

Results. Increased thrombin generation with or without APC ($p<0.001$). Also low TFPI:Ag in 44% of cases. APA status had no effect on ETP or TFPI. Treatment with LMWH normalized these parameters

C. Gardiner, H. Cohen, S. Machin, IJ. Mackie. London

Asymptomatic carriage of the JAK2V6217 mutation is associated with unexplained embryonic and fetal loss during the first pregnancy (OC).

The risk of unexplained fetal loss is dose-dependently related to the expression of the Gly219 variant of the endothelial protein C receptor by the mother, by the father and the couple (OC).

G. Lissalde-Lavigne et al. Nîmes

Du nouveau pour les aPL?

Antiphospholipid antibodies spectrum in women with recurrent fetal loss syndrome

Our aim was to study APA spectrum in patients with recurrent fetal loss syndrome

Methods: 426 patients with recurrent fetal loss syndrome, 150 healthy pregnant women were evaluated for APA, anti: CL, PE, PS, phosphatidylcholine, LA, beta2-GPI, annexin V, prothrombin

Conclusions: The high prevalence of APA (64%) was detected in patients with recurrent fetal loss syndrome. Anti-annexin V prevailed in the APA spectrum

S. Baimuradova, A. Makatsariya, V. Bitsadze, S. Akinshina. Moscow

Anticardiolipin antibodies and outcome of pregnancy – A retrospective 3 year study

Our aims were to investigate whether class of ACA and level affected outcome.

Methods: From 2003-2006, 175 pregnancies in 73 women with IgG or IgM ACA>10GPL or MPL and no other thrombophilia were included in this study. 70 pregnancies were treated with aspirin and/or LMWH and 105 were not. Main outcome measures were preterm delivery, growth restriction, recurrent first trimester miscarriage and intrauterine death in the 2nd or 3rd trimester.

E.J. Ferguson, J. Laird, C. Tait, I. Walker. Glasgow

Anticardiolipin antibodies and outcome of pregnancy – A retrospective 3 year study

Results: There was no significant difference in total adverse outcomes IgG vs IgM except recurrent 1st trimester miscarriage where elevated IgG was more significant ($p<0.05$). For both classes of ACA, there were significantly more adverse outcomes in the untreated groups ($p<0.05$ for IgG, $p<0.01$ for IgM).

Conclusions: Pregnancy outcome is significantly worse in ACA + women who are not treated, even if the levels are lower than the diagnostic criteria for antiphospholipid syndrome (>40 GPL/MPL). Consideration should be given to treating all pregnant women with weakly positive ACA.

The management of high risk pregnant patients with primary APS

TT of high risk pregnancies of women with primary APS is not clear.

Methods: We observed that a group of patients with a history of thromboembolism and triple antibody positivity (IgG ACA, IgG anti-beta2-GP1 and LA), despite taking heparin/aspirin, had a significantly higher risk of unsuccessful pregnancy when compared with the other pregnant APS women. Between 1991 and 2006, 142 patients with APS were followed. Nine (6.3%), who did not respond to the treatment, were shifted to a protocol including plasma exchange (PE) in addition to full dose heparin and low dose aspirin. PE procedures included a session every other day during the first week of treatment, then one session weekly until delivery.

A. Ruffatti, G. De Silvestro, P. Marson, V. Pengo, M. Bortolati, M. Favaro, M. Tonello, D. Minucci. Padua

The management of high risk pregnant patients with primary APS

Results: We had a positive result in 5 cases (55.5%) and in 4 (44.4%) we did not. Moreover, a woman, who had a fetal loss at the 11th week, despite PE therapy, was successfully treated with twice a week Protein A IgG Immunoadsorption in addition to twice a day nadroparin and daily low dose aspirin.

Conclusions: This study suggests that prophylactic apheresis treatments administered along with conventional therapy could be a valuable therapeutic option in high risk pregnant APS women. However, it must be interpreted with caution and more patients need to be followed during pregnancy before such a conclusion may be drawn.

Critères sérologiques pour APS?

"Invitation to a debate on the serological criteria that define the antiphospholipid syndrome"

"Based on the (lack of) evidence discussed, we have the following proposals for the next update of the criteria of APS:

1) Implementation of strict guidelines for the performance of LAC assay,
2) Exclusion of aCL measurements in their current application from the criteria,
3) Limitation of the measurement of aβ2-GPI antibodies to IgG"

M. Galli, G. Reber, P. de Moerloose & P. de Groot. JTH in press

Thèmes

- Thrombophilic markers and pregnancy outcome
- Treatments (LMWHs, fondaparinux, ..)

Utilisation des HBPM (18 P)

Résumé

Résumé : c'est safe, « effective », que ce soit dans la prévention du risque de MTEV et/ou de complications obstétricales ou dans le traitement de la MTEV

HBPM étudiées : enoxaparine, nadroparine, dalteparine, tinzaparine, bemiparine

Tinzaparin once-daily (175 IU/kg)

39 femmes

F. Parent, X. Jaïs, M. Wolf, C. Boyer-Neuman, G. Simonneau, Paris

37 femmes

F. Ni Ainle, N. Appleby, A. Wong, B. Byrne, C. Regan, N. Milner, T. Hassan, B. Nolan, B. White, J. O'Donnell. Dublin

28 femmes (?)

A. Santamaria, J. Vila, A. Marco, J. Mateo, M. Simo, J. Fontcuberta. Barcelona

Well-tolerated, safe and efficacious

For prevention or treatment,

do we have to measure anti-Xa and

if yes, which target level?

Monitoring and dosage modulation of enoxaparin during pregnancy

The need to adapt and monitor LWMH dosage during pregnancy remains controversial.

Methods. 25 women receiving prophylaxis, 40 mg and 60 mg if obese. Treatment initiated at about 11 weeks of gestation. Target anti-Xa 0.3-0.5 for 23 and 0.5-0.7 in 2 high risk.

E.C. Lmbert, B. Dessomme, V. Deneys, C. Hermans. Brussels

Monitoring and dosage modulation of enoxaparin during pregnancy

Average monitoring 4.5/pregnancy.

For 20 patients, initiation dose of 40 mg had to be increased at 60 mg or 80 mg.

Conclusion. Anti-Xa monitoring and dosing adaptations are required to maintain the anti-Xa levels in the therapeutic ranges. DD cannot be used to tailor treatment.

Correct???

Merci Philippe et Jeanne-Yvonne

A randomized, controlled trial to evaluate the efficacy of LMWH on pregnancy outcome of women with previous pregnancy complications

In the absence of RCT, whether or not women with previous OC should benefit from LMWH is not known.

Methods. Inclusion criteria: history of at least 1 PE/HELLP, fetal loss > 15th w, fetal growth restriction or placental abruption; or at least 2 fetal losses < 15th w gestation. Exclusion criteria: history of non-idiopathic OC, thrombosis or aPLA

I,. Martinelli, T. Battaglioli, PM. Mannucci. Milan

Two arms

Randomization within the 12th week of gestation to LMWH (nadroparin 3800 anti-Xa) and intense obstetric surveillance OR intense obstetric surveillance alone.
Monthly visits and periodic blood testing.

Results. Expected in 2 years

Ethique de faire une étude contre placebo?

State of the Art Lecture

Recommandation pour APL ASA-heparin: ACCP 2B (weak, unclear risk/benefit ratio).

Pour les autres thrombophilies, pas d'étude contre placebo: Gris 2004; Live-enox (20% APL) 2005.

Aussi: women with idiopathic recurrent miscarriage: live birth 70-80% (Lindqvist, 2006; Coppens 2007), comparable to heparin-treated thrombophilic women in randomized trials

S. Middeldorp. *JTH* 2007;5:276

Conclusions

Thrombophilia and recurrent miscarriage are weakly associated

No evidence that we should use anticoagulants to prevent with recurrent or late fetal loss

Prognosis of thrombophilic women with recurrent miscarriage is generally good

Trials are underway and recruiting well

S. Middeldorp. JTH SOA 2007

TIPPS study (M. Rodger, Canada)

- Recurrent fetal loss and other pregnancy complications + thrombophilia
- No treatment vs LMWH

ALIFE study (S. Middeldorp)

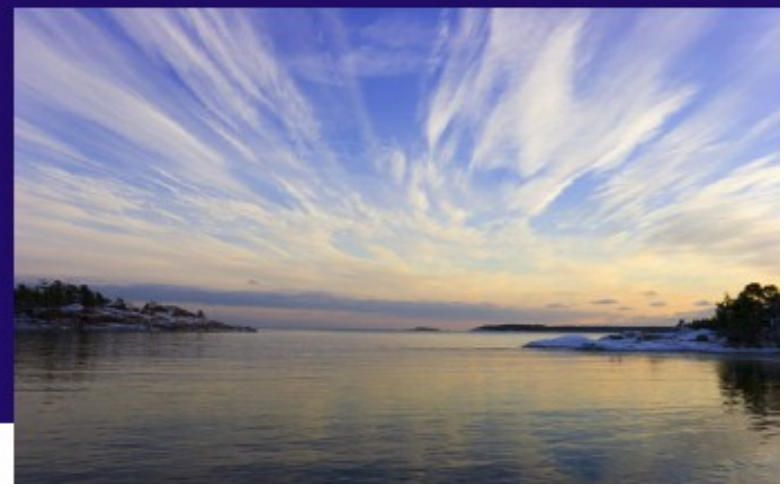
- Recurrent fetal loss - unexplained or with hereditary thrombophilia
- Placebo (for aspirin) vs aspirin vs aspirin + LMWH

SPIN study (R. Farquhason, UK)

- Recurrent fetal loss - unexplained
- No treatment vs aspirin + LMWH

HAPPY study (I. Martinelli, Italy)

- Pregnancy complications
- No treatment vs LMWH



Dalteparin shorten human labor

Protacted labor is a major problem for both mother and baby.

Methods. Labor was studied in 98 nulliparous women treated with dalteparin because of TE during pregnancy or thrombophilia, 142 controls. Primary endpoint was interval from 3-4 cm dilatation and regular contractions until delivery.

Result. Dalteparin shortens labor ($p<0.0001$) and increases myometrial contractililty ($p<0.02$).

M. Hellgren, E. Andersson, B. Byström, M. Edlund, A. Holmberg, A. Klimavicute, M. Sennström, G. Tzortakos, A. Malmström, G. Ekman-Ordeberg. Goteborg, Solna, Lund

Alternative anticoagulation with fondaparinux in pregnant patients with heparin-intolerance

Revue de 8 cas d'intolérance à l'héparine (7 réactions cutanées, 1 HIT), mises sous fondaparinux

Durée moyenne de ttt: 76 j. Aucune complication.

Conclusions. « In spite of these promising results, the use of fondaparinux should be limited to pregnant women with no further treatment options »

M. Schindewolf, C. Daemgen, H. Mani, E. Lindhof-Last. Frankfurt

Conclusions

Vision très restreinte et subjective du sujet

Tests d'hémostase chez des femmes qui ont fait des complications obstétricales et qui n'ont pas d'histoire de MTE en clinique???

Traitements : un certain rationnel pour utiliser ASA et/ou HBPM (indépendamment du risque de MTEV pour qques cas), safe, alternatives, attente de RCT

« Un conseil »

Ne viens pas, mens, dis que tu es très malade, que tu as trop mangé de chocolat (belge), que tu as raté le train ou l'avion, mais surtout ne viens pas.

Ce serait un acte profondément masochiste

Merci Philippe


J'ETAIS EN RETARD A CAUSE DES GREVES A LA S.N.C.F... J'AI PERDU MON BOULOT A CAUSE DES GREVES A LA S.N.C.F... IL NE ME RESTE QU'A MOURIR, MAIS JE NE PEUX PAS A CAUSE DES GREVES A LA S.N.C.F.!
...

Efficacy of enoxaparin in preventing adverse feto-maternal events in carriers of AT, PC, PS deficiencies

Data about prophylactic HBPM in women with AC deficiencies to decrease OC are very limited.

Methods. 32 women with a history of unexplained fetal loss. 8 women: treatment with enoxaparin 4000 IU once a day since pregnancy test positive until 4-6 w of puerperium. 7/8 women were 0 parae.

E. Grandone, V. de Stefano, E. Rossi, F. Cappucci, T. Za, D. Colaizzo, G. Tisciua, M. Margaglione. Rome, Foggia.

Conclusions

Thrombophilia and recurrent miscarriage is weakly associated

- Thrombophilia slightly increases risk for recurrent miscarriage

Thrombophilia can be considered a component cause for recurrent miscarriage in some women

Potential mechanisms are being elucidated

No evidence that we should use anticoagulants in women with recurrent or late fetal loss

- Prognosis of thrombophilic women with recurrent miscarriage is generally good
- Trials are underway and recruiting well

S. Middeldorp. JTH SOA 2007

Efficacy of enoxaparin in preventing adverse feto-maternal events in carriers of AT, PC, PS deficiencies

Results and **Conclusion**. Before referral live births in 27/95 pregnancies (28.4%) and after referral 7/8 had a successful delivery (p=0.001).

Screening for thrombophilia in a retrospective study of 320 women with pregnancy complications

Retrospective study of women with > than 3 EFL (31.7%), LFL (35.8%), IUGR (15.9%), PE (10.7%) and PA (5.9%)

Results. 4.9% FVL h or FIIG20210A h; 3 were AT (I or II), 3 PC deficient and 3 were VL/II combined (2.8%); 5 women had a new successful pregnancy with aspirin in all cases and LMWH in 4/5

Conclusions. Our study suggests that rare thrombophilic disorders should be screened in women with pregnancy complications

M. Slaoui, N. Ajzenberg, M. Dauge, C. Scarabin, M. Guillin, D. Mahieu-Caputo. Paris