ΚΩΝΣΤΑΝΤΙΝΟΣ Ε. ΚΩΣΤΑΡΑΣ

Μαιευτήρ – Γυναικολόγος
Διδάκτωρ Παν/μίου Αθηνών
Ιατρός Μονάδας Υποβοηθούμενης Αναπαραγωγής ΙΑΣΩ

Η αντιπηκτική αγωγή και οι ενδείξεις της, στην αναπαραγωγική διαδικασία της γυναίκας.

Το παράδοξο της αιμόστασης στην κύηση

Η επιτυχής έκβαση της κύησης απαιτεί:

* Αποφυγή της αιμορραγίας
  - κατά την εμφύτευση CTB-KTB
  - κατά την ενδοαγγειακή διείσδυση και αναμόρφωση των σπειροειδών αρτηριών της μήτρας
  - κατά το 3ο στάδιο του τοκετού
* Διατήρηση φυσιολογικής μητροπλακουντιακής κυκλοφορίας

Practice Bulletin No138 2013 AGOG

Ο φθαρτός της μήτρας έχει καθοριστικό ρόλο στην αιμόσταση της μητροπλακουντιακής μονάδος π.χ. :

- εξωμήτριος κύηση
- στιφρός πλακούντας
- αποκόλληση πλακούντα

Practice Bulletin No138 2013 AGOG

1/1600 τοκετούς VTE

Κατά την κύηση :

- Αύξηση της δυνατότητας της πήξεως
- Μείωση της αντιπηκτικής δράσης και ινοδώλυσης

Επιπλέον επιβάρυνση με:

- Η μήτρα πιέζει την κάτω κοίλη και πυελικές φλέβες, ορμονική διαστολή φλεβών, υπερλιπιδαιμία, αυξημένη αντίσταση στην ινσουλίνη

Practice Bulletin No138 2013 AGOG

ΘΡΟΜΒΟΦΙΛΙΑ

- Ισχυρή συσχέτιση με το VTE
- Συγγενής θρομβοφιλία
- Αμφισβητούμενη συσχέτιση με την μητροπλακουντιακή θρόμβοση
- Αποβολές
- Προεκλαμψία
- IUGR
- Αποκόλληση πλακούντα
- Συσχέτιση με το APS

Practice Bulletin No138 2013 AGOG

Αποβολές

- Σποραδικές έως 25% των κυήσεων<10w
  Καθ΄ έξην έως
- 5% ζευγαριών 1ου τριμήνου
- 2% ζευγαριών 2ου τριμήνου<24w
- ↑ με την αύξηση της ηλικία της μητέρας
- ↑ με την αύξηση της ηλικίας του πατέρα
- ↑ με τον αριθμό των αποβολών

RCOG Guideline No 17 2011

Practice Committee ASRM FERTILITY STERILITY VOL 98 No 5/NOV 2012
Evaluation and treatment of recurrent pregnancy loss

APS

- 20% των καθ᾽ έξην αποβολών
- 2% στο γενικό πληθυσμό
- 90% αποβολές χωρίς θεραπεία

RCOG Guideline No 17 2011

APS

- ⬇φθαρτοποίηση
- ⬇διαφοροποίηση
- ⬇διείσδυση **τροφοβλάστης**
- ⬆απόπτωση
- ⬆Ενεργοποίηση του συμπληρώματος C5a

Βλάβη πλακούντα

εμβρυϊκός θάνατος, αποκόλληση, προεκλαμψία, πρόωρος τοκετός, VTE

L. REGAN HI RISCK PREGNANCY EDIT ELSEVIER 2011

Αποβολές 2ου τριμήνου

- ισχυρή συσχέτιση με V, 20210, ⇓ S
- Ενώ για το 1ο τρίμηνο είναι αντιφατικά

RCOG Guideline No 17 2011


D. JAMES Hi Risk PREGNANCY EDIT ELSEVIER 2011

PCO

- **PAI-1** promotor ινσουλινοεξαρτώμενος
- Αντίσταση στην ινσουλίνη
- ⬇ινοδώλυση = ⬇εμφύτευση
- Μετάλλαξη 4G/4G

L. REGAN HI RISCK PREGNANCY EDIT ELSEVIER 20

Προεκλαμψία

- 20% των κυήσεων παρουσιάζει ένα είδος υπέρτασης
- 7% στις υγιείς πρωτοτόκες
- Νόσος της 1ης κύησης στο ζευγάρι
- Πατέρας με ιστορικό προεκλαμψίας έχει διπλάσια πιθανότητα με διαφορετική σύντροφο

G Dekker Hi Risk PREGNANCY EDIT ELSEVIER 2011

Προεκλαμψία

- Ηλικία, ↑ βάρος, υπέρταση, πολύδυμος, Σ.Δ., προϋπάρχουσα ΘΜΦ, φλεγμονώδη νοσήματα, πολυτόκες, χαμηλό βάρος γέννησης , χρήση IVF
- 14% υποτροπή
- 50% υποτροπή σε πρόωρη προεκλαμψία ή χρόνια υπέρταση

G Dekker Hi Risk PREGNANCY EDIT ELSEVIER 2011

IUGR

Έως το 9% των νεογνών

Αιτιολογία:

- Πλακουντιακή
- Μη πλακουντιακή

G Dekker Hi Risk PREGNANCY EDIT ELSEVIER 2011

IUGR

Συσχετίζεται με ιστορικό :

- προεκλαμψίας
- θνησιγεννούς IUGR,
- χρήση IVF και χαμηλό βάρος
- «Αγγειοπάθεια» μητέρας
- Σ.Δ. , Σ.Ε.Λ., Υπέρτασης , Νεφρικής Νόσου, APS

IUGR

Συσχετίζεται με:

- Παθολογία της τρέχουσας κύησης
- Αιμόρροια
- Προεκλαμψία
- Υπέρταση
- Χαμηλό βάρος
- Χαμηλό PAPP-A

RCOG Guideline No 31 2013

IUGR

- Έναρξη ασπιρίνης σε γυναίκες με αυξημένη πιθανότητα προεκλαμψίας, IUGR πριν τις 16w, μειώνει την πιθανότητα εμφάνισής της.
- Δεν υπάρχουν επαρκή στοιχεία για την σύστασή της

RCOG Guideline No 31 2013

Αποκόλληση πλακούντα

- 1% των κυήσεων απαιτεί τοκετό
- Επί ιστορικού αυξάνει την πιθανότητα 15-20 φορές

OBSTETRICS GYNECOLY 7th edit AGOG 2011

Ενδομήτριος Θάνατος >24w

3,9 / 1.000 ζωντανές γεννήσεις

30% IUGR

Παχυσαρκία, ηλικία, προεκλαμψία, αποκόλληση πλακούντα, ρήξη μήτρας, πρόπτωση ομφαλίδος Σ.Δ. ,συγγενείς ανωμαλίες

RCOG Guideline No 55 2010

Τι κοινό υπάρχει;

- Ανεπαρκής διείσδυση της CTB στο φθαρτό, στα σπειροειδή αγγεία και μεταμόρφωσή τους στο 50%
- Αυξημένη ενεργοποίηση ενδοθηλίου
- Αυξημένη φλεγμονώδης αντίδραση

Μητροπλακουντιακή κυκλοφορία

- PGI 2 / TXA2 Διαταραχή
- Συσσώρευση PLT
- Εναπόθεση θρομβίνης και ινώδους
- Θρομβώσεις και έμφρακτα του πλακούντα, φθαρτού
- Αποκόλληση, IUGR, προεκλαμψία

G Dekker Hi Risk PREGNANCY EDIT ELSEVIER 2011

Αναγνωρίζεται η κοίτη του πλακούντα ως βασικός παράγων για την φυσιολογική ή παθολογική εξέλιξη της ανθρώπινης κύησης

Η παθολογία των αγγείων ως μηχανισμός της παθολογίας στην κύηση.
ΑΝΕΠΑΡΚΗΣ ΑΓΓΕΙΟΓΕΝΕΣΗ ΘΡΟΜΒΩΣΕΙΣ ΚΑΙ Η ΑΝΕΠΑΡΚΗΣ ΜΕΤΑΜΟΡΦΩΣΗ ΤΩΝ ΣΠΕΙΡΟΕΙΔΩΝ ΑΡΤΗΡΙΩΝ ΟΔΗΓΟΥΝ ΣΕ ΙΣΧΑΙΜΙΑ ΤΟΥ ΠΛΑΚΟΥΝΤΑ ΚΑΙ ΤΗΣ ΜΗΤΡΑΣ

R.ROMERO p.280 Placenta Bed Disorders ,edit .Gambridge 2010

Συνέπειες Ισχαιμίας

Βαρύτητα και χρονική στιγμή έναρξης

Κλινικά

- Θάνατος του εμβρύου (αντιαγγειακός παράγων
- IUGR = συμβιβασμος + μειωμένη παροχή

Θρεπτικών συστατικών

-Υπέρταση - Προεκλαμψία (αντιπροπιστικά)

- Πρόωρος τοκετός (επιτάχυνση ωρίμανσης)

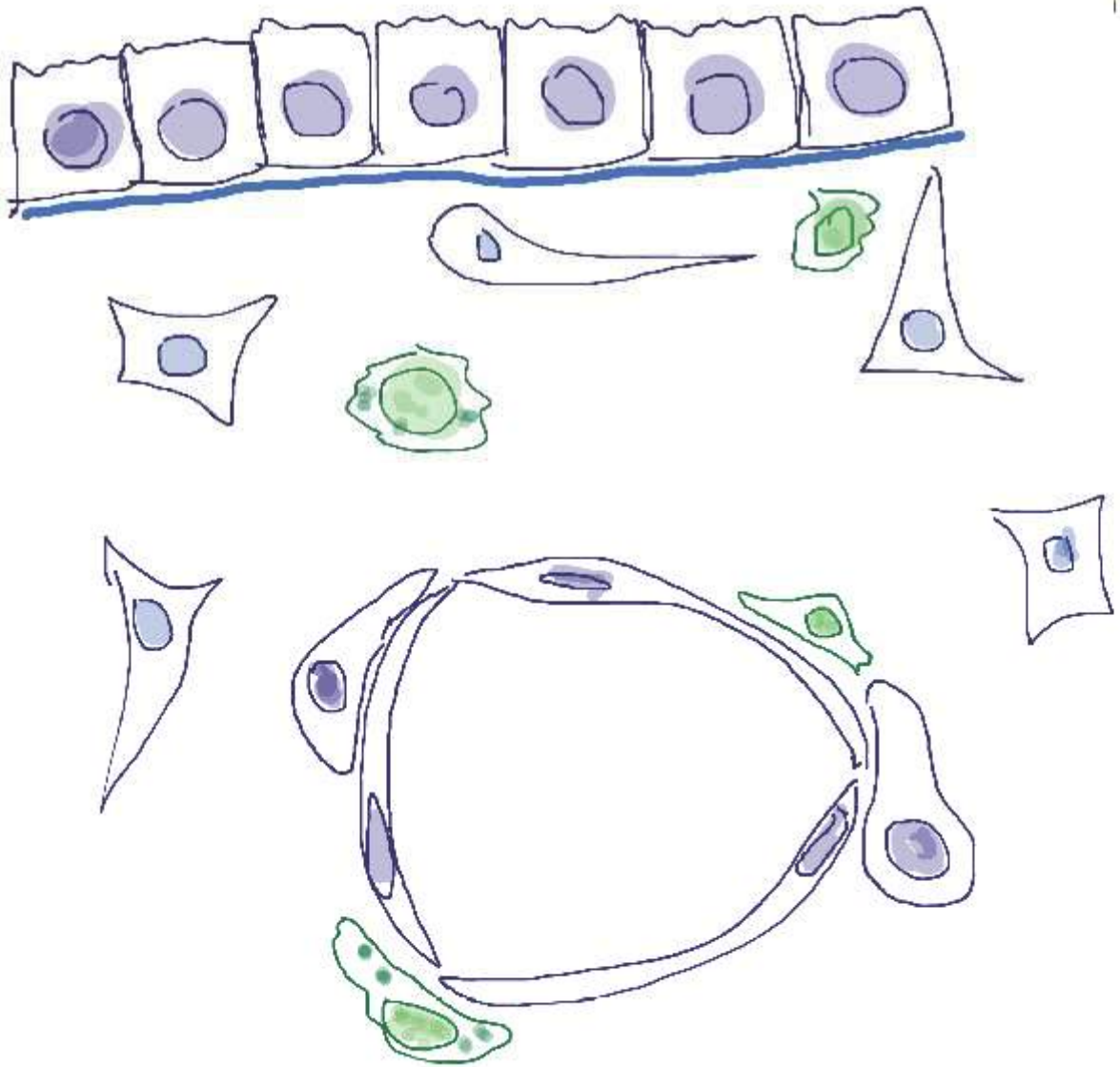
R.ROMERO p.280 Placenta Bed Disorders ,edit .Gambridge 2010

Έμβρυο CTB - Μητέρα/ Φθαρτός Αγγειακή Μεταμόρφωση σε 4 στάδια

1. Συμμετοχή φθαρτού
2. Ενδαγγειακή φάση τροφοβλάστης
3. Ενδοτειχωματική φάση τροφοβλάστης
4. Μητρική μερική επιδιόρθωση

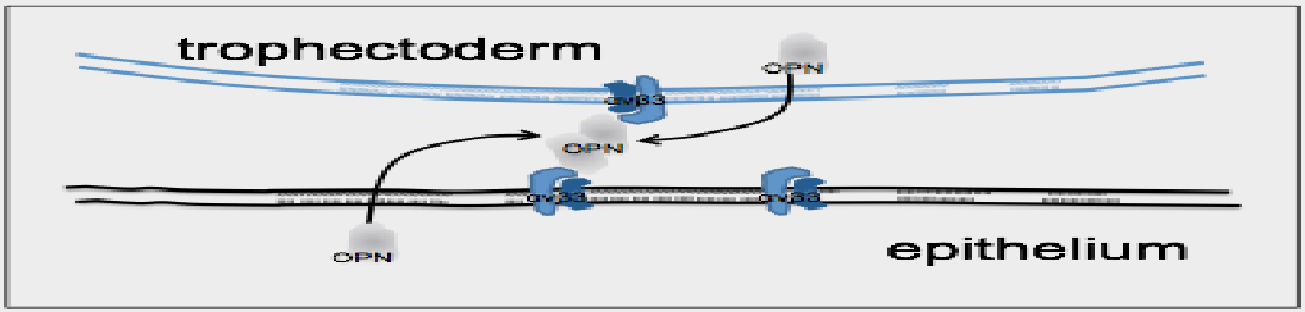
Η ανεπαρκής μεταμόρφωση ως συνέπεια ανεπαρκούς συνεργασίας μητέρας-εμβρύου.
Η ανεπαρής φθαρτοποίηση ως αίτιο.

Placental Bed Vascular Disorder p. 26, Cambridge edition 2010


Epithelium
Stroma
Vasculature
Myometrium

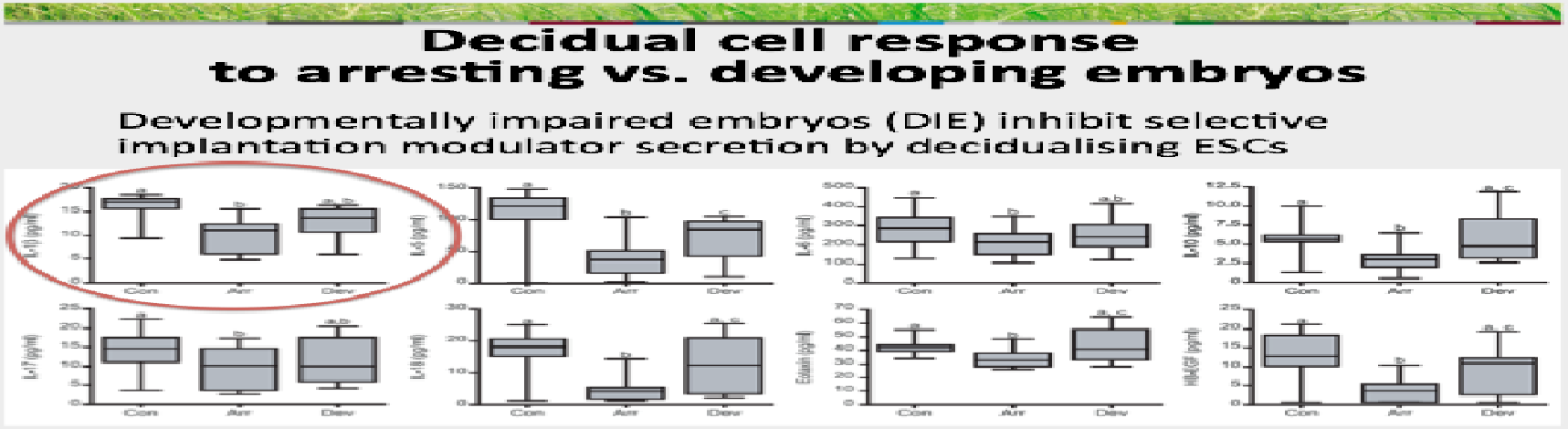
Η παραγωγή των Ιντεγκρινών προοάγεται από την Προγεστερόνη

The interaction between OPN and integrin αvβ3 mediates early embryo attachment



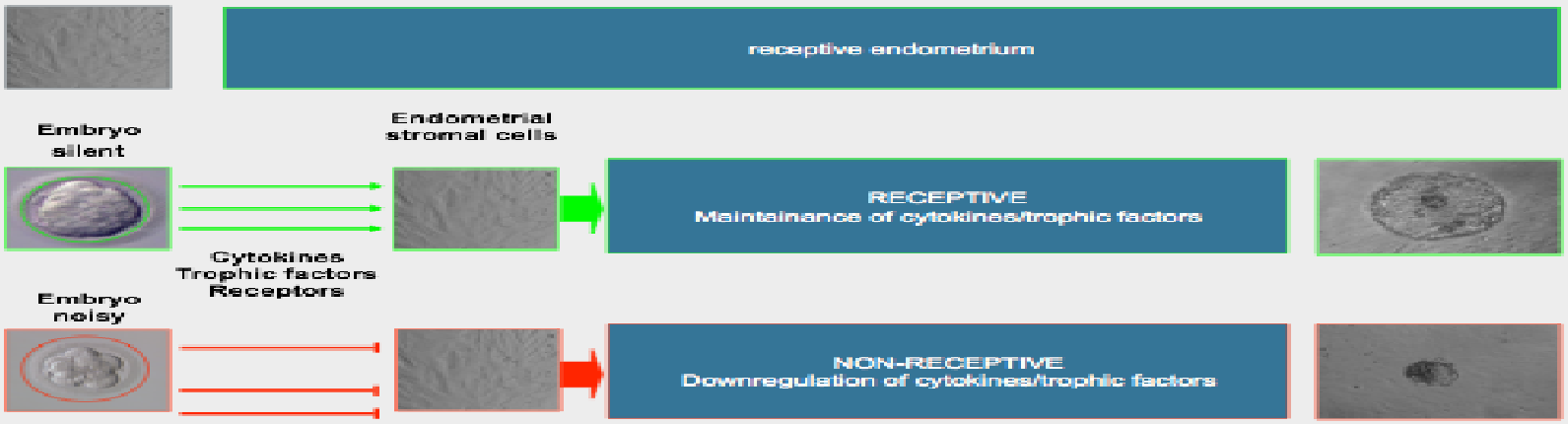
Kang YJ, Forbes K, Carver J, Aplin JD. The role of the osteopontin-integrin αvβ3 interaction at implantation: functional analysis using three different in vitro models. Hum Reprod 2014;29:739-49.

Ο φθαρτός ενεργά "δε συνεργάζεται" - Απορρίπτει τα ανώμαλα έμβρυα



Teklenburg G et al. PLoS ONE: April 2010; e10258

Natural selection of embryos: decidualising endometrial stromal Cells serve as sensors of quality on implantation



Teklenburg G et al. PLoS ONE: April 2010; e10258

Many normal embryos also miscarry

- At least some of these failures are caused by maternal abnormalities
- These may include:
  - poor decidualisation
  - spiral arteries that resist remodelling
  - failure of immune recognition
  - abnormalities of the blood clotting system

Aplin 2014 “black box of implantation” EXCEMED

Φθαρτοποιήση - Προγεστερόνη

Το "ECM" αλλάζει χαρακτηριστικά¨

α) Υπερτερούν Collagen IV, Laminin, Heparan Sulphate => διευκολύνουν τη διείσδυση της CTB

β) Αποικισμός με ανοσολογικά κύτταρα NK, Μακροφάγα, Τ- Λεμφοκύτταρα

γ) Ανάπτυξη σπειροειδών αρτηριών FGFb: αγγειογεννετικός, (+ E2, - P) VEGF: αυξάνει διαπαιρατότητα και υπερτροφία ενδοθηλίου (+ E2, χαμ.O2)
PDGF: αγγειογεννετικός

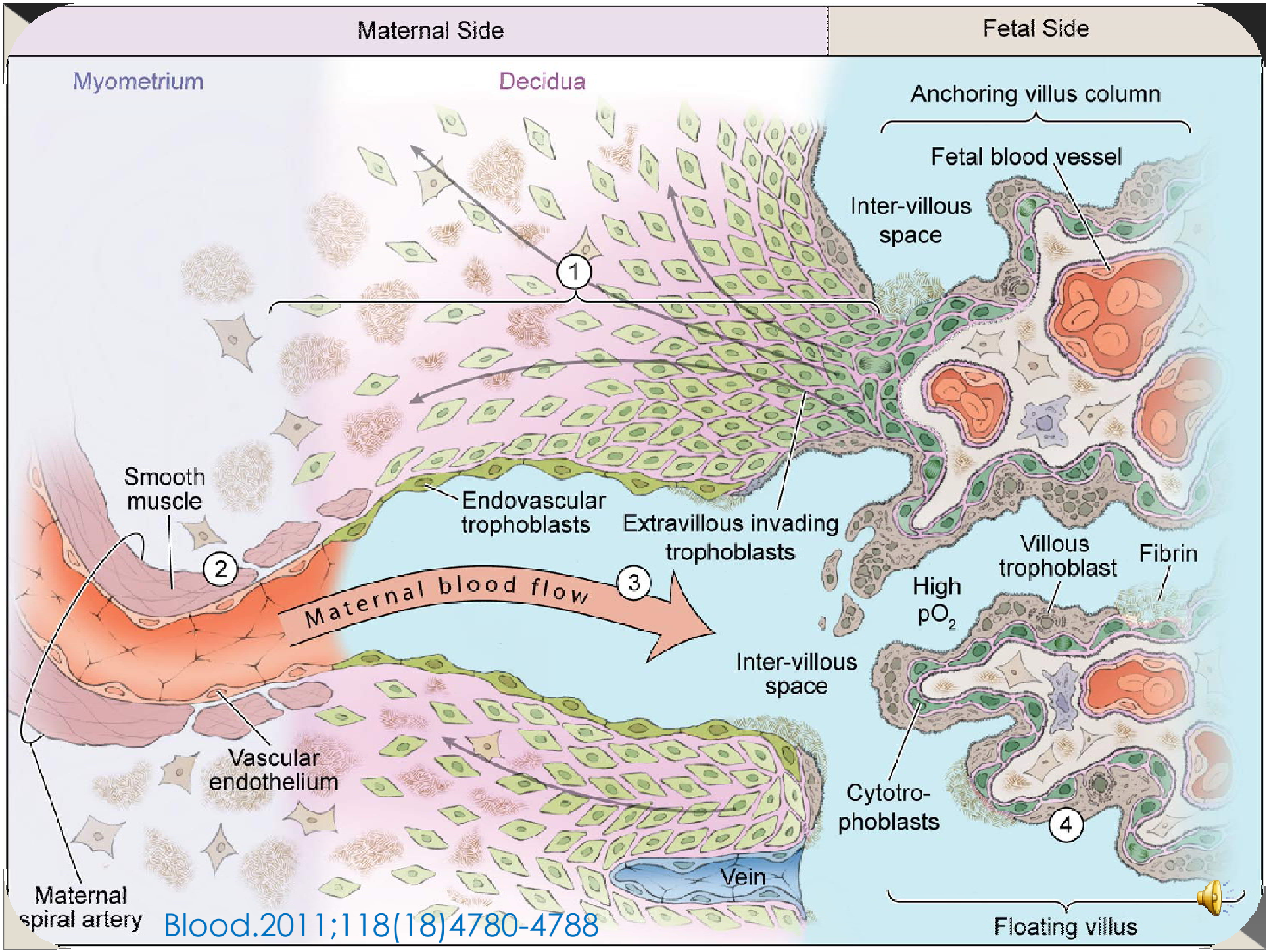
Η νεοαγγειογέννεση αναστέλλεται από παθήσεις με μικροαγγειοπάθει (ΣΔ, Α/Υ)

PMervil et.al "Folia Histochemica et Cytobiologica", Vol. 47, No.5, 2009

Η διείσδυση της τροφοβλάστης δεν είναι παθητική διαδικασία

Αλλαγές στην έκφραση των ιντεγκρινών καθώς βαθαίνει στο ECM
α6β4 (laminin)=> α5β1 (fibronectin)=>
α1β1(laminin-collagen IV)
Τα τροφοβλαστικά κύτταρα συνδέονται με υποδοχείς στα διάφορα συστατικά του ECM.

PMervil et.al "Folia Histochemica et Cytobiologica", Vol. 47, No.5, 2009



Blood.2011;118(18)4780-4788

Διείσδυση Σπειροειδών Αρτηριών

- 1η διείσδυση: 5η-8η w
- Ο EVCTS καλύπτει εξωτερικά τα τριχοειδή του φθαρτού και ενδομητρικούς κλάδους των σπειρωειδών σχηματίζοντας “κέλυφος”.

- Τα κύτταρα του τροφοβλαστικού ιστού κινούνται από το εξωτερικό προς το εσωτερικό των αγγείων. Έμβολα καταλαμβάνουν τον αυλό των αγγείων επιτρέπουν τη διάχυση πλάσματος αυξάνουν το PO2 ενδαγγειακά = μειωμένη υπεροξείδωση, αυξ. PGI2, μειωμ. TXA2, αύξηση του NO.
- => ΑΓΓΕΙΟΔΙΑΣΤΟΛΗ

PMervil et.al “Folia Histochemica et Cytobiologica”, Vol. 47, No.5, 2009

MMP's

Τα τροφοβλαστικά κύτταρα εκκρίνουν MMS για την προτεόλυση του ECM.

Ο φθαρτός εκκρίνει αναστολείς TIMP's.

"TGF-β"

Αναστέλλουν τον πολλαπλασιασμό και τη διείσδυση

Ο β1 από την τροφοβλάστη αυξάνει το ECM (collagen-fibrin) και το T1MP1 και διεγύρει την α5β1 ιντεγκρίνει με αποτέλεσμα την ισχυρότερη σύνδεση με το ECM.

=>Αναστολή διείσδυσης.

PMervil et.al "Folia Histochemica et Cytobiologica", Vol. 47, No.5, 2009

Χαμηλό O2 στον πλακούντα 8η-12η w

- Αυξάνει την αγγειογέννεση
- Προστατεύει από τις ελεύθερες ρίζες O_2
- Παρά την ύπαρξη εμβόλων τροφοβλάστης δεν σχηματίζονται θρόμβοι
- **Trombomodulin** (ενδοθήλιο) διεγείρει τη C και αναστέλλει την θρόμβωση
- **Tissue factor** (φθαρτός) από την PRG
- ⇧ την θρομβίνη ινώδους ⇧παρουσία του VII

PMervil et.al "Folia Histochemica et Cytobiologica", Vol. 47, No.5, 2009

Τα έμβολα του τροφοβλαστικού ιστού απουσιάζουν στις αποβολές του 1ου τριμήνου. Διαλύονται μετά από 8-13 w

PMervil et.al "Folia Histochemica et Cytobiologica", Vol. 47, No.5, 2009

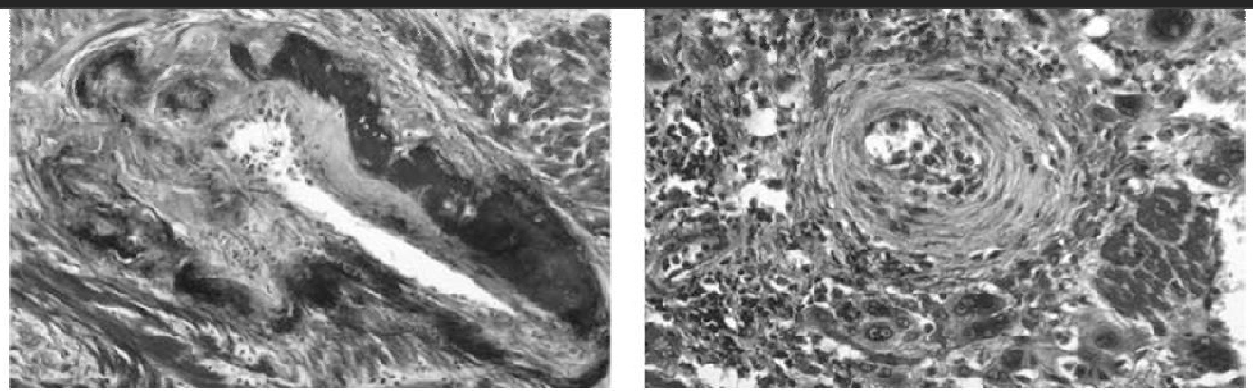
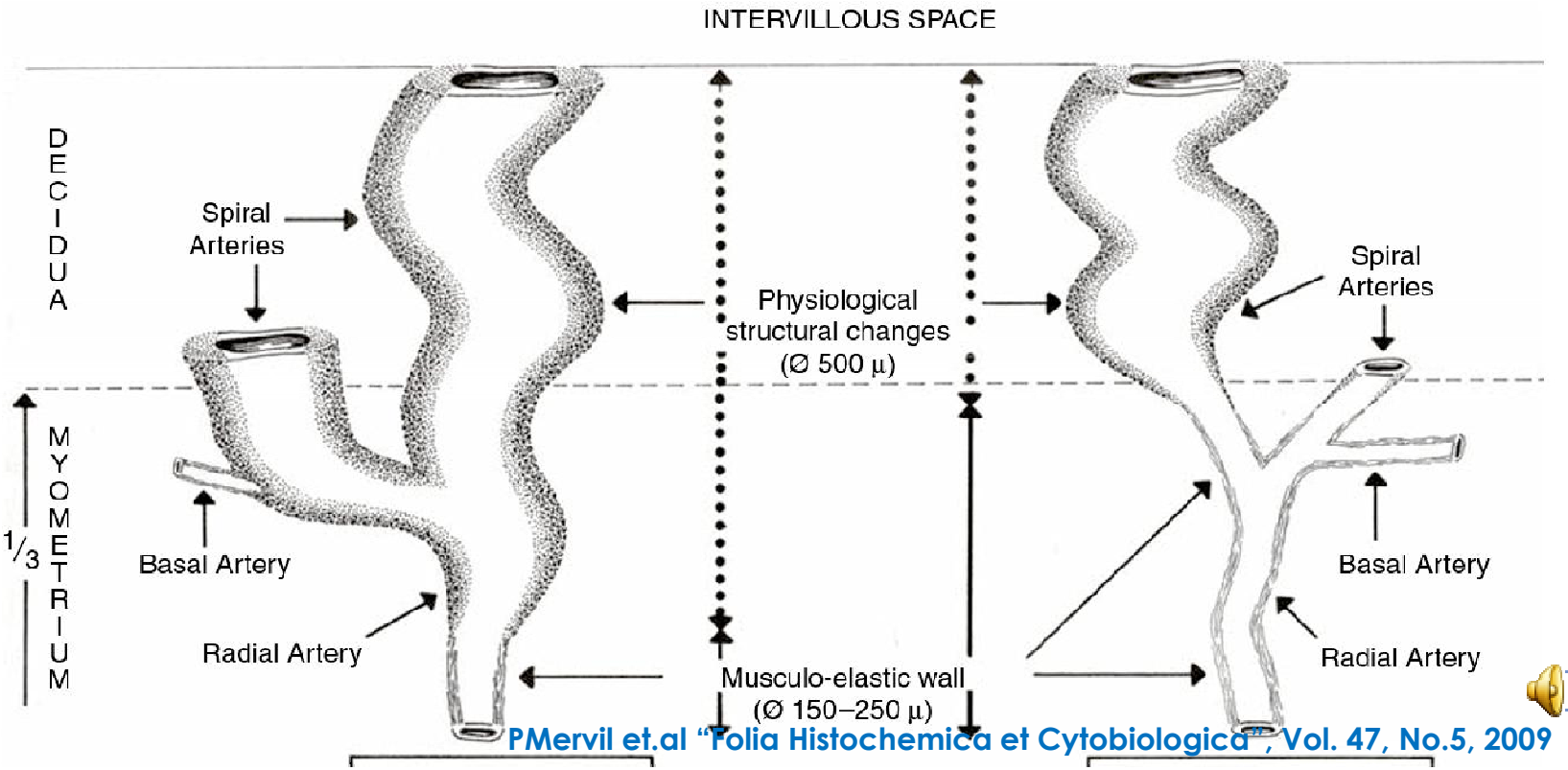


Fig. 3.1 (A) Uteroplacental artery showing marked distension and replacement of the muscular and elastic tissue in the wall by fibrinoid and invaded trophoblast. (B) A spiral artery in the junctional zone myometrium in severe preeclampsia showing absence of physiological changes and surrounded by interstitial trophoblast (Masson trichrome). See plate section for color version.



PMervil et.al "Folia Histochemica et Cytobiologica", Vol. 47, No.5, 2009

2η Διείσδυση μεταξύ 13-18 w

Κύτταρα των εμβόλων αποικίζουν την εσωτερική επιφάνεια του αυλού των αγγείων ενδοτοιχωματικά.
Έτσι προοδευτικά το ενδοθήλιο και οι λύες μυϊκές ίνες εξαφανίζονται και αντικαθίστανται από το ινώδες.
Τα τροφοβλαστικά κύτταρα αναπτύσσουν ενδοθηλιακό φαινότυπο (VCAM-1, PECAM-1).
Έτσι τα αγγεία έχουν μικρότερη αντίσταση και αυξημένη χωρητικότητα.
Εξαφανίζονται τα notches από τις μητριαίες έως τις 26w

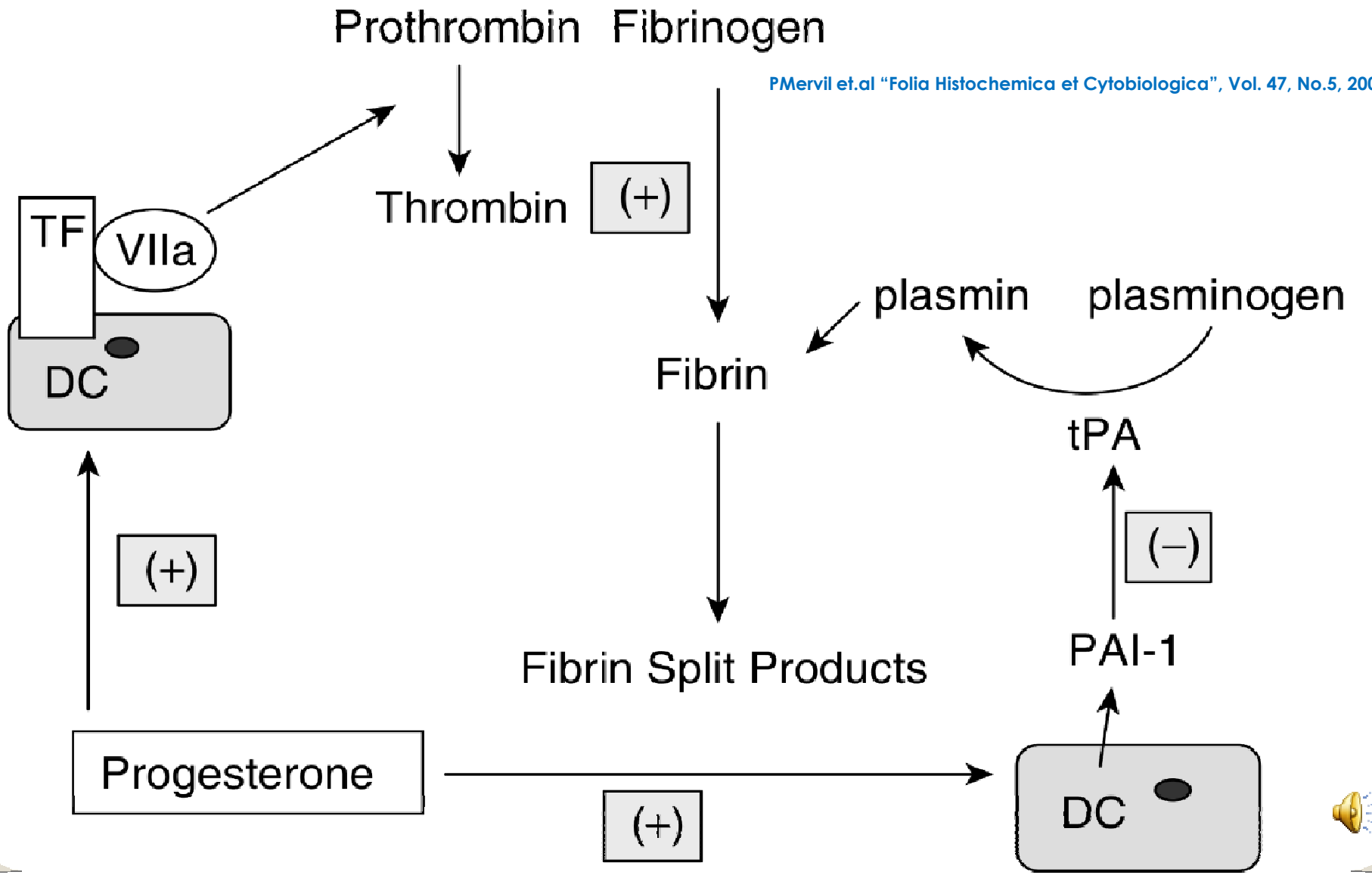
PMervil et.al "Folia Histochemica et Cytobiologica", Vol. 47, No.5, 2009

Αγγειοκινητικοί Παράγοντες

- ET(endothelin):αγγειοσυσπαστικός - Enkephalinase (+P)
- στο IUGR και στην Προεκλαμψία
- NO(ενδοθήλιο): αγγειοδιασταλτικός - αυξημένος στην κύηση
- E2: αγγειοδιαστολή απ'ευθείας ή μέσω ET-NO
- P: αγγειοδιαστολή ή αγγειοσύσπαση (σε χαμηλά επίπεδα)
- PG's: TXA2 και PGF2 (αγγειοσύσπαση) μέσω των PLT's
- PGI2: αγγειοδιαστολή - ενδοθήλιο, τροφοβλάστης
- ACTH: ισχυρό αγγειοδιαστολτικό- αυξάνει στην προεκλαμψία και στο IUGR
- CRF: ισχυρότερο αγγειοδιασταλτικό
- Η βλάβη του ενδοθηλίου μειώνει την παραγωγή τους.

PMervil et.al "Folia Histochemica et Cytobiologica", Vol. 47, No.5, 2009

Εγκατάσταση αιματικής ροής στο μεσολάχνειο χώρο 8-12 w



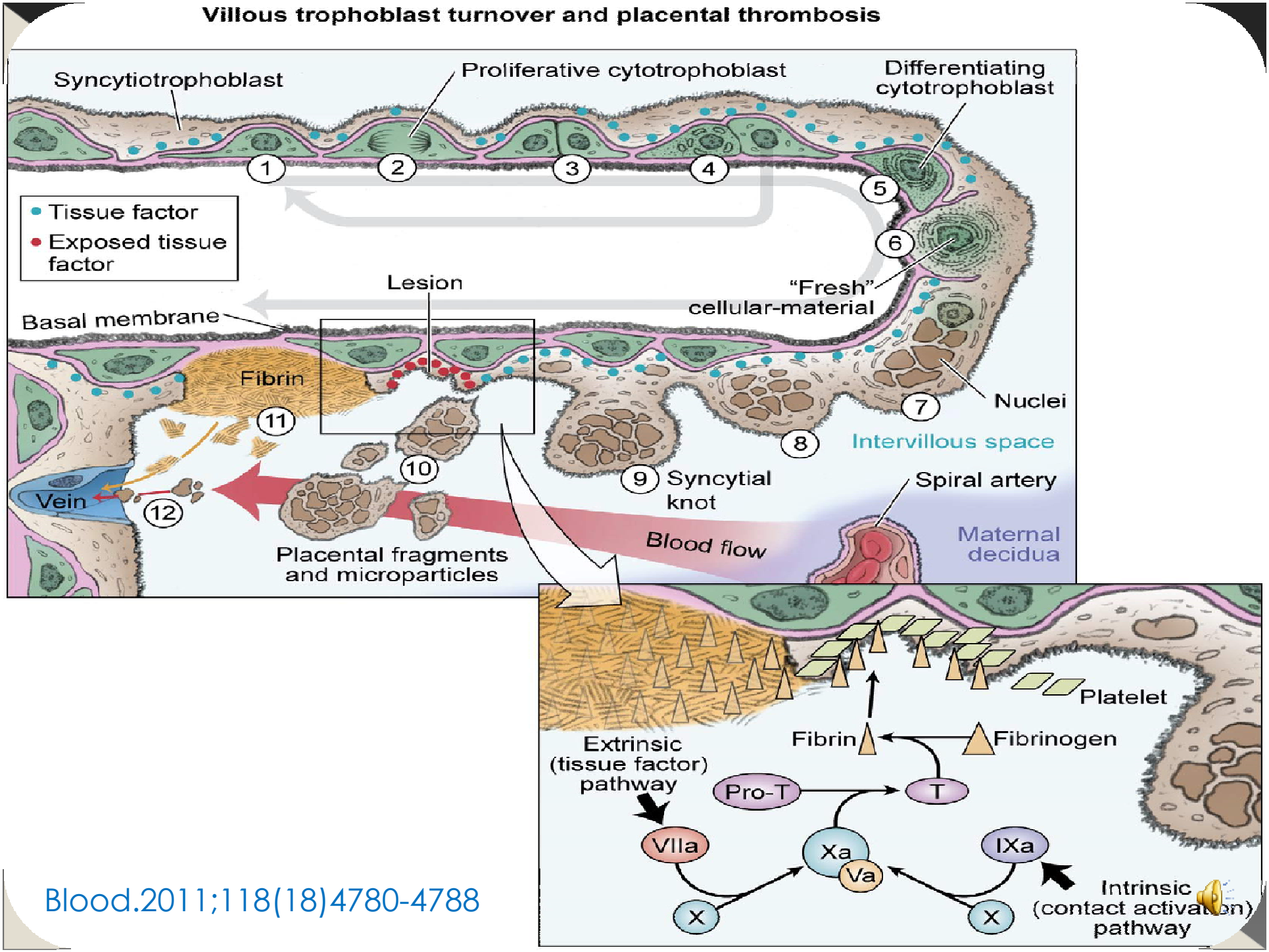
Is heparin a placental anticoagulant in high-risk pregnancies?

John C. P. Kingdom[1,2] and Sascha Drewlo[2]

[1]Maternal-Fetal Medicine Division, Department of Obstetrics & Gynecology; and [2]Program in Development and Fetal Health, Samuel Lunenfeld Research Institute at Mount Sinai Hospital, University of Toronto, Toronto, ON

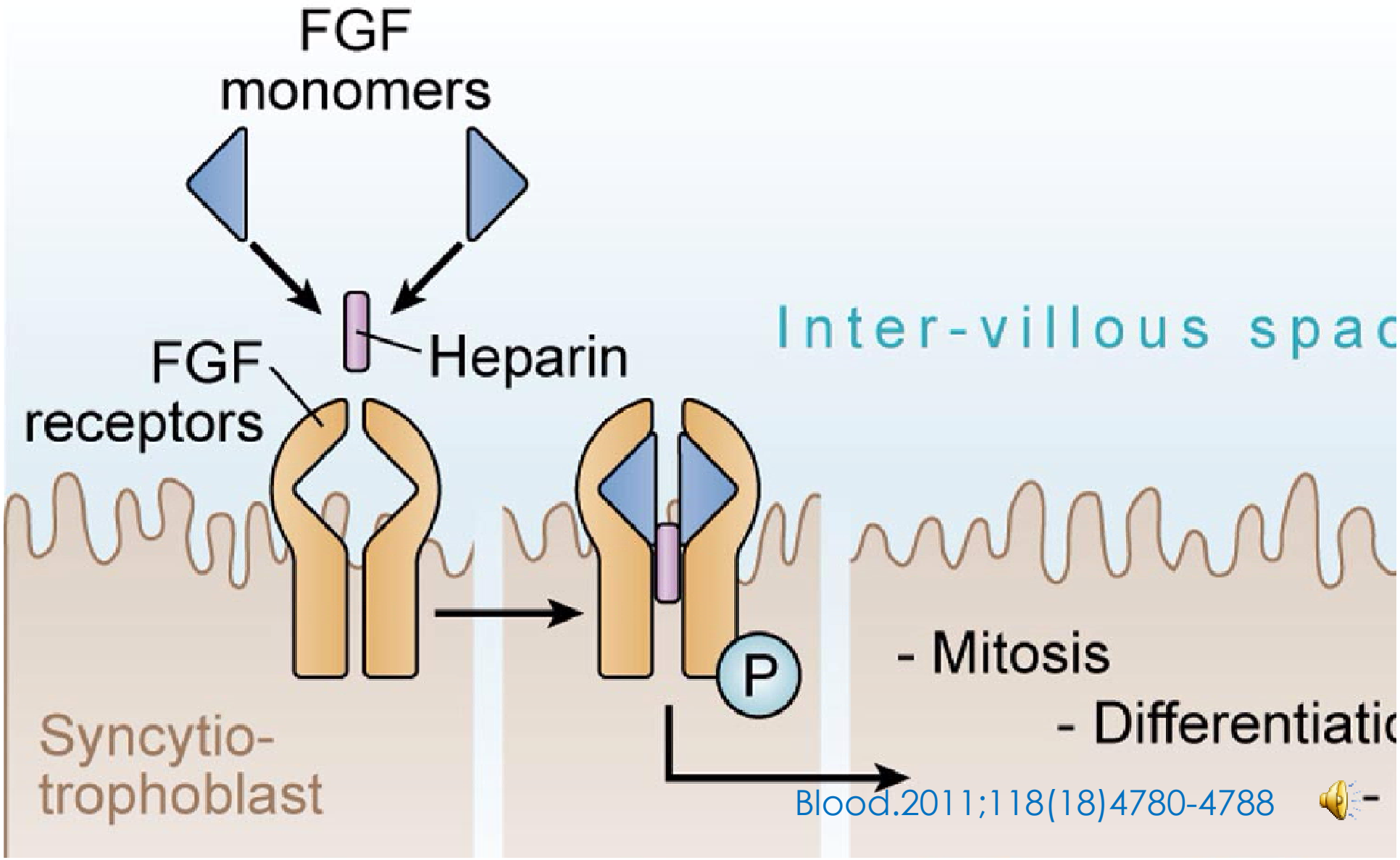
Randomized control trials show beneficial effects of heparin in high-risk pregnancies to prevent preeclampsia and intrauterine growth restriction. However, the lack of placental pathology data in these trials challenges the assumption that heparin is a placental anticoagulant. Recent data show that placental infarction is probably associated with abnormalities in development of the placenta, characterized by poor maternal perfusion and an abnormal villous trophoblast compartment in contact with maternal blood, than with maternal thrombophilia. At-risk pregnancies may therefore be predicted by noninvasive prenatal testing of placental function in mid-pregnancy. Heparin has diverse cellular functions that include direct actions on the trophoblast. Dissecting the non–anticoagulant actions of heparin may indicate novel and safer therapeutic targets to prevent the major placental complications of pregnancy. (*Blood*. 2011;118(18):4780-4788)

Blood.2011;118(18)4780-4788

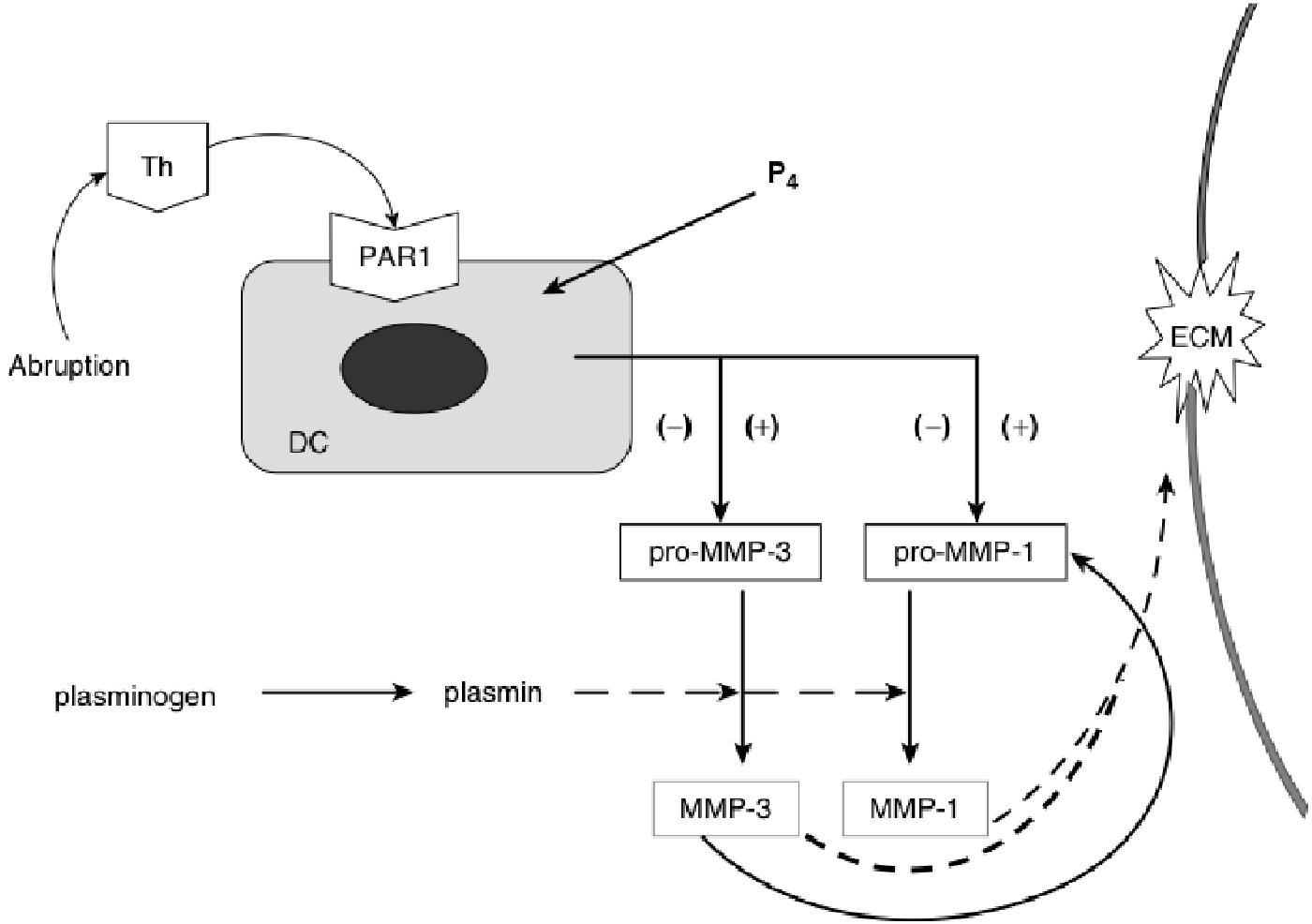


Blood.2011;118(18)4780-4788

Heparin as a co-factor for FGF signaling



Blood.2011;118(18)4780-4788


Th
PAR1
P_4
Abruption
DC
(–)
(+)
(–)
(+)
ECM
pro-MMP-3
pro-MMP-1
plasminogen
plasmin
MMP-3
MMP-1

Human Reproduction, Vol.27, No.5 pp. 1499–1503, 2012
Advanced Access publication on February 21, 2012 doi:10.1093/humrep/des041

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

No evidence that assisted reproduction increases the risk of thrombosis: a Danish National cohort study

A.T. Hansen[1,*], U.S. Kesmodel[2], S. Juul[3], and A.M. Hvas[1]

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BACKGROUND: Case reports have reported venous and arterial thromboses in women undergoing assisted reproduction. No large systematic studies on the risk of thrombosis have been published. The objective of our study was to investigate whether the risk of thrombosis is increased in women undergoing assisted reproduction.

METHODS: A national register-based cohort study was conducted on all women undergoing IVF or ICSI treatment in Denmark from 1994 to 2005. Data were obtained from the National Patient Registry and the IVF Registry. Women with prior malignant or cardiovascular disease were excluded. Thrombosis occurring within the first 6 and 12 months after assisted reproduction was considered potentially related to the treatment. Thromboses during pregnancy as well as the pregnancy-related diagnoses were excluded from the statistical analysis. The incidence rates of venous and arterial thromboses were compared with previously published estimates of the risk of thrombosis among young Danish women.

RESULTS: We analyzed 30 884 Danish women undergoing 75 141 treatments from 1994 to 2005. The mean age of the women at first treatment was 32.3 years. The delivery rate per cycle was 22%. The incidence rate ratio, with 95% confidence interval (CI), of venous thrombosis within 6 months was 0.95 (CI: 0.38–1.95). The incidence rate ratio of arterial thrombosis within 6 months was 0.36 (CI: 0.04–1.30).

CONCLUSIONS: Our study showed no evidence that assisted reproduction increases the risk of thrombosis.

Key words: assisted reproduction / ovarian hyperstimulation syndrome / thrombosis

Human Reproduction

ABOUT THIS JOURNAL CONTACT THIS JOURNAL SUBSCRIPTIONS CURRENT ISSUE ARCHIVE SEARCH

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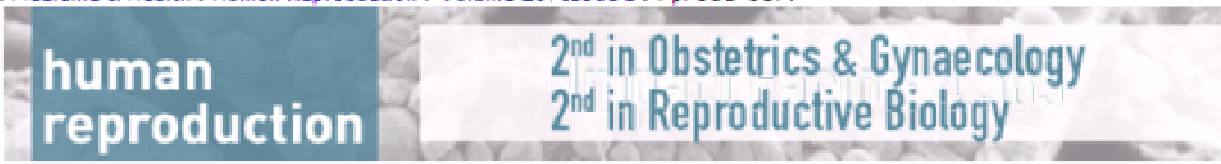

Increased venous thrombosis incidence in pregnancies after *in vitro* fertilization

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Abstract

STUDY QUESTION Is venous thrombosis risk increased in pregnancies after *in vitro* fertilization?

SUMMARY ANSWER The venous thrombosis incidence was significantly increased in pregnancies after *in vitro* fertilization; especially in the first trimester and in the first 6 weeks post-partum.

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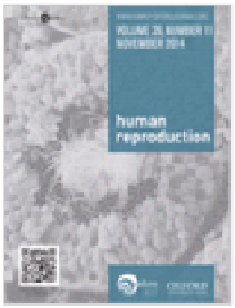

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The Journal

Review article

Thrombophilia and outcomes of assisted reproduction technologies: a systematic review and meta-analysis

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Thrombophilia has been associated with pregnancy complications and recurrent miscarriage. The aim of this systematic review was to evaluate the controversial association between thrombophilia and failures of assisted reproduction technology (ART). A systematic search of the literature for studies reporting on thrombophilia in women undergoing ART up to April 2011 yielded 33 studies (23 evaluating anti-phospholipid antibodies, 5 inherited thrombophilia, and 5 both) involving 6092 patients. Overall, methodologic quality of the studies was poor. Combined results from case-control studies showed that factor V Leiden was significantly more prevalent among women with ART failure compared with fertile parous women or those achieving pregnancy after ART (odds ratio = 3.08; 95% confidence interval, 1.77-5.36). The prothrombin mutation, methylenetetrahydrofolate reductase mutation, deficiency of protein S, protein C, or anti-thrombin were all not associated with ART failure. Women with ART failure tested more frequently positive for anti-phospholipids antibodies (odds ratio = 3.33; 95% confidence interval, 1.77-6.26) with evidence of high degree of between-study heterogeneity (I^2 = 75%; P < .00001). Prospective cohort studies did not show significant associations between thrombophilia and ART outcomes. Although case-control studies suggest that women experiencing ART failures are more frequently positive for factor V Leiden and anti-phospholipid antibodies, the evidence is inconclusive and not supported by cohort studies. (*Blood*. 2011;118(10):2670-2678)

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REVIEW

Effect of heparin on the outcome of IVF treatment: a systematic review and meta-analysis

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Abstract The effect of heparin on IVF outcome has been widely debated in the literature. A systematic review and meta-analysis of the published literature was conducted to evaluate the effect of heparin treatment on IVF outcome. Searches were conducted on MEDLINE, EMBASE, Cochrane Library and Web of Science and identified 10 relevant studies (five observational and five randomized) comprising 1217 and 732 IVF cycles, respectively. The randomized studies included small numbers of women and exhibited high methodological heterogeneity. Meta-analysis of the randomized studies showed no difference in the clinical pregnancy rate (RR 1.23, 95% CI 0.97–1.57), live birth rate (RR 1.27, 95% CI 0.89–1.81) implantation rate (RR 1.39, 95% CI 0.96–2.01) and miscarriage rate (RR 0.77, 95% CI 0.24–2.42) in women receiving heparin compared with placebo during IVF treatment. However, meta-analysis of the observational studies showed a significant increase in the clinical pregnancy rate (RR 1.83, 95% CI 1.04–3.23, $P = 0.04$) and live birth rate (RR 2.64, 95% CI 1.84–3.80, $P < 0.0001$). The role of heparin as an adjuvant therapy during IVF treatment requires further evaluation in adequately powered high-quality randomized studies.

KEYWORDS: heparin, IVF, observational studies, pregnancy, randomized controlled trials

In conclusion, this systematic review demonstrates that the role of adjuvant heparin therapy during IVF has not been adequately evaluated by current literature. On the basis of published literature, the group of patients who could benefit from heparin therapy could not be identified with certainty. Specifically, the role of heparin in subfertile women with known thrombophilia and those with unex- plained recurrent IVF implantation failure warrants further evaluation with adequately powered randomized studies.

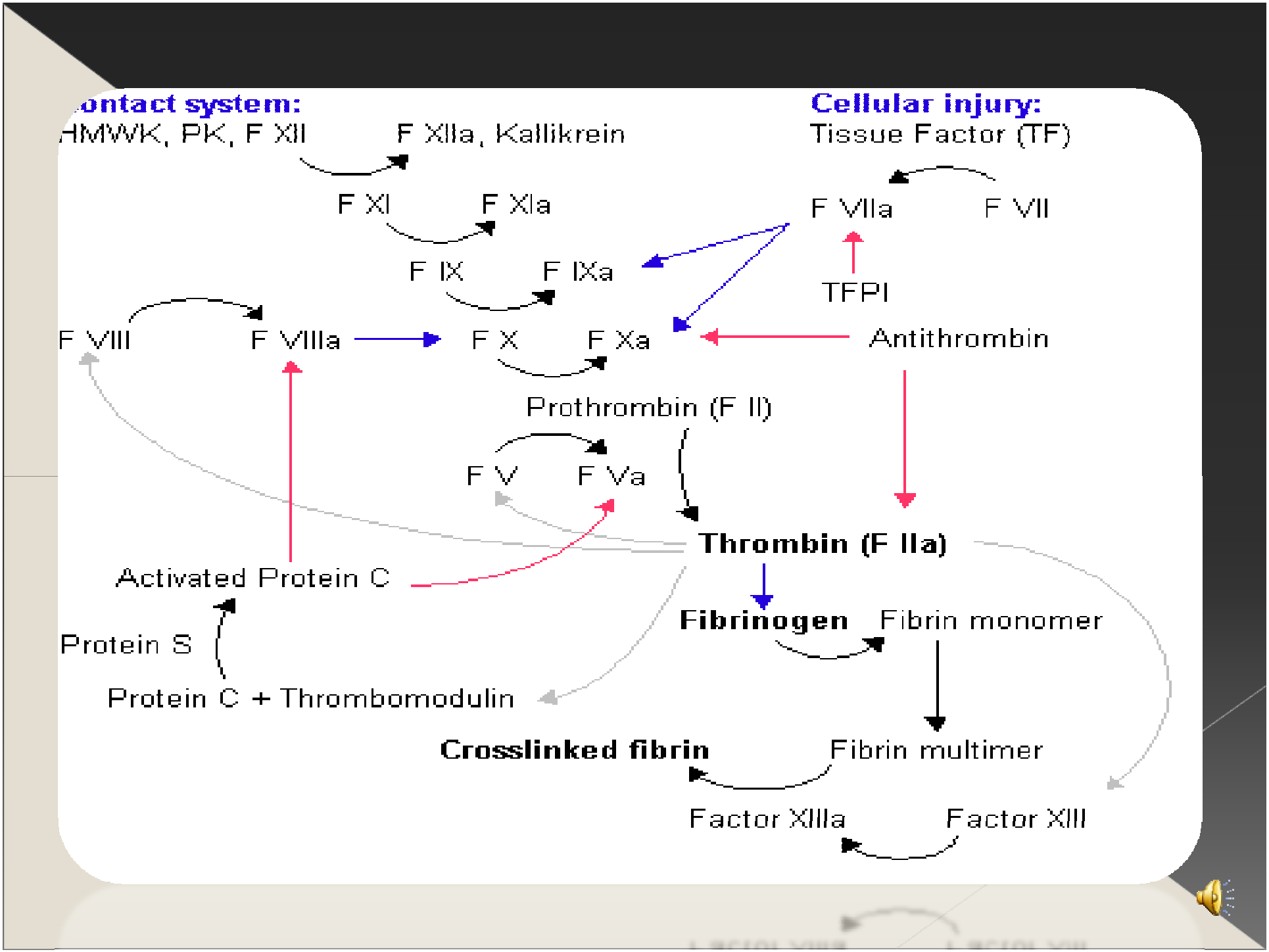
ontact system:
HMWK, PK, F XII
F XIIa, Kallikrein
F XI
F XIa
F IX
F IXa
F VIII
F VIIIa
F X
F Xa
Cellular injury:
Tissue Factor (TF)
F VIIa
F VII
TFPI
Antithrombin
Prothrombin (F II)
F V
F Va
Thrombin (F IIa)
Activated Protein C
Protein S
Protein C + Thrombomodulin
Fibrinogen
Fibrin monomer
Crosslinked fibrin
Fibrin multimer
Factor XIIIa
Factor XIII

Table 1: Risk factors for venous thromboembolism in pregnancy

Timeframe	Factors
Pre-existing	Previous venous thromboembolism Thrombophilia: *Heritable*: Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden Prothrombin gene G20210A *Acquired (antiphospholipid syndrome)*: Persistent lupus anticoagulant Persistent moderate/high-titre anticardiolipin antibodies or β_2 glycoprotein 1 antibodies Medical comorbidities (e.g. heart or lung disease, SLE, cancer, inflammatory conditions (inflammatory bowel disease or inflammatory polyarthropathy), nephrotic syndrome (proteinuria > 3 g/day), sickle cell disease,[36] intravenous drug user Age > 35 years Obesity (BMI > 30 kg/m²) either prepregnancy or in early pregnancy Parity ≥ 3 Smoking Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes) Paraplegia
Obstetric	Multiple pregnancy, assisted reproductive therapy Pre-eclampsia Caesarean section PPH (> 1 litre) requiring transfusion } Prolonged labour, mid-cavity rotational operative delivery
New-onset/transient Potentially reversible[a]	Surgical procedure in pregnancy or puerperium (e.g. ERPC, appendicectomy, postpartum sterilisation) Hyperemesis, dehydration Ovarian hyperstimulation syndrome Admission or immobility (≥ 3 days' bed rest) e.g. symphysis pubis dysfunction restricting mobility Systemic infection (requiring antibiotics or admission to hospital) e.g. pneumonia, pyelonephritis, postpartum wound infection Long-distance travel (> 4 hours)

BMI = body mass index; ERPC = evacuated PPH = postpartum haemorrhage; evacuation of retained products of conception; SLE = systemic lupus erythematosus

[a] May develop at later stages in gestation than the initial risk assessment or may resolve and therefore continuing individual risk assessment is important

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These data and recent international guidelines[16] support a recommendation to stratify women with previous VTE into the following categories, which are described in Figure 1 and Appendix II:

- **Very high risk**
  Women with recurrent VTE associated with either antithrombin deficiency or the antiphospholipid syndrome (who will often be on long-term oral anticoagulation). These women require thromboprophylaxis with higher-dose LMWH (either high prophylactic (12-hourly) or weight-adjusted (75% of treatment dose)[16,46] (see Table 3) antenatally and for 6 weeks postpartum or until converted back to warfarin after delivery. These women require specialist management by experts in haemostasis and pregnancy.
- **High risk**
  Women in whom the original VTE was unprovoked, idiopathic or related to estrogen (estrogen-containing contraception or pregnancy) or who have other risk factors, a family history of VTE in a first-degree relative (suggestive of thrombophilia) or a documented thrombophilia. These women require thromboprophylaxis with LMWH antenatally and for 6 weeks postpartum.
- **Intermediate risk**
  Women in whom the original VTE was provoked by a transient major risk factor that is no longer present and who have no other risk factors. In these women, thromboprophylaxis with LMWH can be withheld antenatally, provided that no additional risk factors are present (in which case they should be offered LMWH). They require close surveillance for the development of other risk factors. They should be offered thromboprophylaxis with LMWH for 6 weeks postpartum.

Any woman with objective documentation of previous VTE should have a careful history documented and, if appropriate, should undergo testing for both heritable and acquired thrombophilia, preferably before pregnancy. Where objective documentation is not available, the previous diagnosis of VTE can be assumed in cases where the woman gives a good history and received prolonged (more than 6 weeks) therapeutic anticoagulation.

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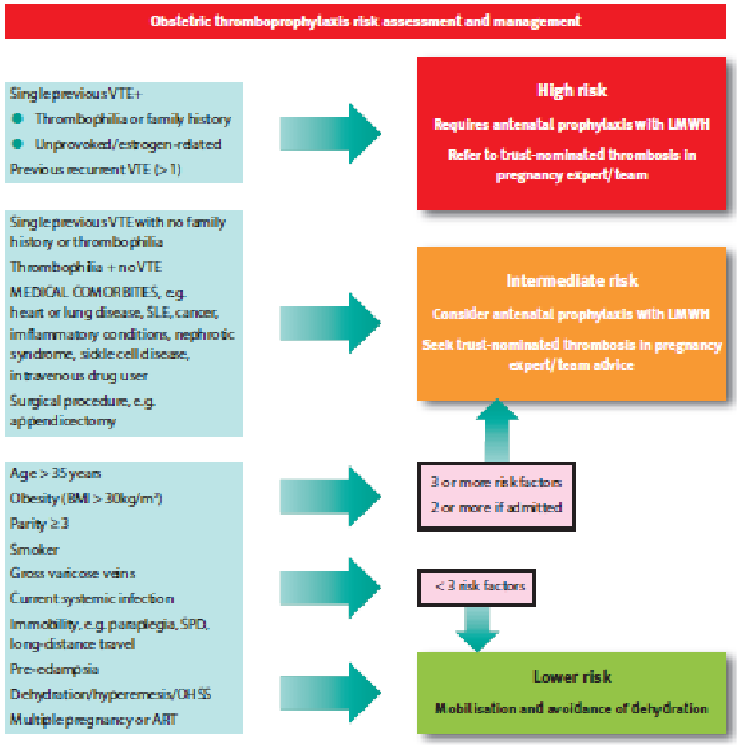
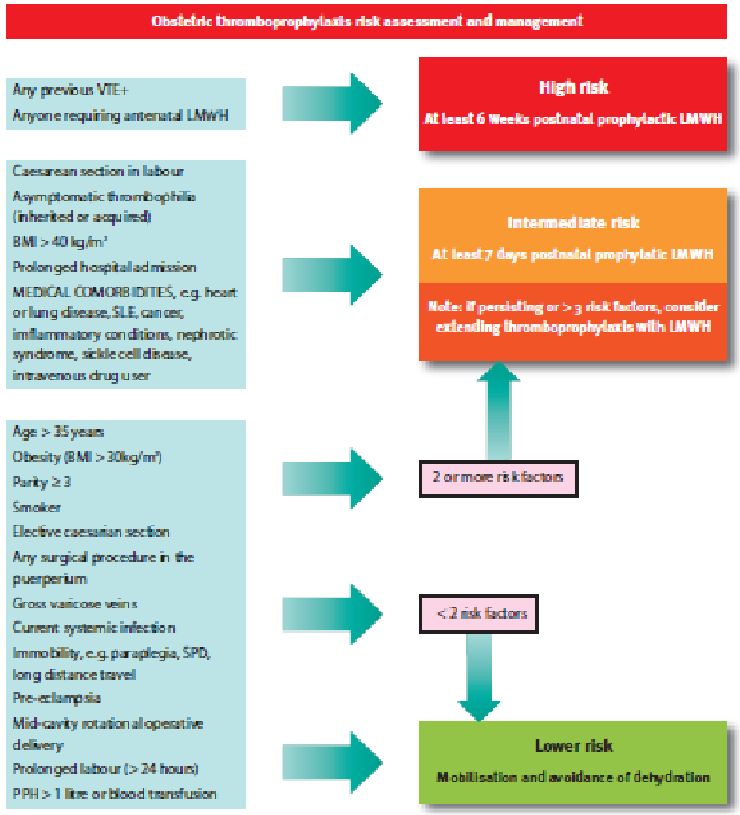
Antenatal assessment and management (to be assessed at booking and repeated if admitted)



Antenatal and postnatal prophylactic dose of LMWH
Weight: < 50 kg = 20 mg enoxaparin/2500 units dalteparin/3500 units tinzaparin daily
Weight: 50–90 kg = 40 mg enoxaparin/5000 units dalteparin/4500 units tinzaparin daily
Weight: 91–130 kg = 60 mg enoxaparin/7500 units dalteparin/7000 units tinzaparin daily
Weight: 131–170 kg = 80 mg enoxaparin/ 10000 units dalteparin/9000 units tinzaparin daily
Weight: > 170 kg = 0.6 mg/kg/day enoxaparin; 75 units/kg/day dalteparin/75 units/kg/day tinzaparin

Key
ART = assisted reproductive therapy, BMI = body mass index (based on booking weight), gross varicose veins = symptomatic, above the knee or associated with phlebitis/oedema/skin changes, Immobility = ≥ 3 days, LMWH = low-molecular-weight heparin, OHSS = ovarian hyperstimulation syndrome, PPH = postpartum haemorrhage, SLE = systemic lupus erythematosus, SPD = symphysis pubis dysfunction with reduced mobility, thrombophilia = inherited or acquired, long-distance travel = > 4 hours, VTE = venous thromboembolism

Postnatal assessment and management (to be assessed on delivery suite)



Key
ART = assisted reproductive therapy, BMI = body mass index (based on booking weight), gross varicose veins = symptomatic, above the knee or associated with phlebitis/oedema/skin changes, immobility = ≥ 3 days, LMWH = low-molecular-weight heparin, OHSS = ovarian hyperstimulation syndrome, PPH = postpartum haemorrhage, SLE = systemic lupus erythematosus, SPD = symphysis pubis dysfunction with reduced mobility, thrombophilia = inherited or acquired, long-distance travel = > 4 hours, VTE = venous thromboembolism

Figure 1. Obstetric thromboprophylaxis risk assessment and management

Table 1. Risk of Venous Thromboembolism With Different Thrombophilias

	Prevalence in General Population (%)	VTE Risk per Pregnancy *(No History)* (%)	VTE Risk per Pregnancy *(Previous VTE)* (%)	Percentage of All VTE	References
Factor V Leiden heterozygote	1–15	0.5–1.2	10	40	1–4
Factor V Leiden homozygote	<1	4	17	2	1–4
Prothrombin gene heterozygote	2–5	<0.5	>10	17	1–4
Prothrombin gene homozygote	<1	2–4	>17	0.5	1–4
Factor V Leiden/prothrombin double heterozygote	0.01	4–5	>20	1–3	1–4
Antithrombin III activity (<60%)	0.02	3–7	40	1	1, 5, 6
Protein C activity (<50%)	0.2–0.4	0.1–0.8	4–17	14	1, 5, 7
Protein S free antigen (<55%)	0.03–0.13	0.1	0–22	3	1, 8–10

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► *Who are candidates for thrombophilia evaluation?*

Screening for thrombophilias is controversial. It is useful only when results will affect management decisions, and is not useful in situations where treatment is indicated for other risk factors. Screening may be considered in the following clinical settings:

- A personal history of venous thromboembolism that was associated with a nonrecurrent risk factor (eg, fractures, surgery, and prolonged immobilization). The recurrence risk among untreated pregnant women with such a history and a thrombophilia was 16% (odds ratio, 6.5; 95% confidence interval, 0.8–56.3) (55).
- A first-degree relative (eg, parent or sibling) with a history of high-risk thrombophilia.

In other situations, thrombophilia testing is not routinely recommended. Testing for inherited thrombophilias in women who have experienced recurrent fetal

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Table 2. How to Test for Thrombophilias ⇦

Thrombophilia	Testing Method	Is Testing Reliable During Pregnancy?	Is Testing Reliable During Acute Thrombosis?	Is Testing Reliable With Anti-coagulation?
Factor V Leiden mutation	Activated protein C resistance assay (second generation)	Yes	Yes	No
	If abnormal: DNA analysis	Yes	Yes	Yes
Prothrombin *G20210A* mutation	DNA analysis	Yes	Yes	Yes
Protein C deficiency	Protein C activity (<60%)	Yes	No	No
Protein S deficiency	Functional assay (<55%)	No*	No	No
Antithrombin deficiency	Antithrombin activity (<60%)	Yes	No	No

*If screening in pregnancy is necessary, cutoff values for free protein S antigen levels in the second and third trimesters have been identified at less than 30% and le than 24%, respectively.

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*Postpartum treatment levels should be greater or equal to antepartum treatment. Treatment of acute VTE and management of antiphospholipid syndrome are addressed in other Practice Bulletins.

†Low-risk thrombophilia: factor V Leiden heterozygous; prothrombin *G20210A* heterozygous; protein C or protein S deficiency.

‡First-degree relative with a history of a thrombotic episode before age 50 years, or other major thrombotic risk factors (eg, obesity or prolonged immobility).

§High-risk thrombophilia: antithrombin deficiency; double heterozygous for prothrombin *G20210A* mutation and factor V Leiden; factor V Leiden homozygous or prothrombin *G20210A* mutation homozygous.

‖Surveillance without anticoagulation therapy is supported as an alternative approach by some experts.

...e 4. Recommended Thromboprophylaxis for Pregnancies Complicated by Inherited Thrombophilias*

Clinical Scenario	Antepartum Management	Postpartum Management
Low-risk thrombophilia† without previous VTE	Surveillance without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum anticoagulation therapy if the patient has additional risks factors‡
Low-risk thrombophila with a family history (first-degree relative) of VTE	Surveillance without anticoagulation therapy	Postpartum anticoagulation therapy or intermediate-dose LMWH/UFH
Low-risk thrombophilia† with a single previous episode of VTE—Not receiving long-term anticoagulation therapy	Prophylactic or intermediate-dose LMWH/UFH or surveillance without anticoagulation therapy	Postpartum anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ without previous VTE	Surveillance without anticoagulation therapy, or prophylactic LMWH or UFH	Postpartum anticoagulation therapy
High-risk thrombophilia§ with a single previous episode of VTE or an affected first-degree relative—Not receiving long-term anticoagulation therapy	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH regimen	Postpartum anticoagulation therapy, or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be at least as high as antepartum treatment)
No thrombophilia with previous single episode of VTE associated with transient risk factor that is no longer present—Excludes pregnancy- or estrogen-related risk factor	Surveillance without anticoagulation therapy	Postpartum anticoagulation therapy‖
No thrombophilia with previous single episode of VTE associated with transient risk factor that was pregnancy- or estrogen-related	Prophylactic-dose LMWH or UFH¶	Postpartum anticoagulation therapy
No thrombophilia with previous single episode of VTE without an associated risk factor (idiopathic)—Not receiving long-term anticoagulation therapy	Prophylactic-dose LMWH or UFH¶	Postpartum anticoagulation therapy
Thrombophilia or no thrombophilia with two or more episodes of VTE—Not receiving long-term anticoagulation therapy	Prophylactic or therapeutic-dose LMWH or Prophylactic or therapeutic-dose UFH	Postpartum anticoagulation therapy or Therapeutic-dose LMWH/UFH for 6 weeks
Thrombophilia or no thrombophilia with two or more episodes of VTE—Receiving long-term anticoagulation therapy	Therapeutic-dose LMWH or UFH	Resumption of long-term anticoagulation therapy

...reviations: LMWH, low molecular weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

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WOMEN'S HEALTH CARE PHYSICIANS

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 132, DECEMBER 2012

(Replaces Practice Bulletin Number 118, January 2011)

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder defined by the presence of characteristic clinical features and specified levels of circulating antiphospholipid antibodies (Box 1 and Box 2). Diagnosis requires that at least one clinical and one laboratory criterion are met. Because approximately 70% of individuals with APS are female (1), it is reasonably prevalent among women of reproductive age. Antiphospholipid antibodies are a diverse group of antibodies with specificity for binding to negatively charged phospholipids on cell surfaces. Despite the prevalence and clinical significance of APS, there is controversy about the indications for and types of antiphospholipid tests that should be performed in order to diagnose the condition. Much of the debate results from a lack of well-designed and controlled studies on the diagnosis and management of APS. The purpose of this document is to evaluate the data for diagnosis and treatment of APS.

Box 1. Laboratory Criteria for the Diagnosis of Antiphospholipid Syndrome

1. Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart. It is interpreted as either present or absent. Testing for lupus anticoagulant is ideally performed before the patient is treated with anticoagulants, or
2. Anticardiolipin antibody of immunoglobulin G (IgG) and/or immunoglobulin M isotype in serum or plasma, present in medium or high titer (ie, greater than 40 GPL or MPL, or greater than the 99th percentile), on two or more occasions, at least 12 weeks apart, or
3. Anti-β_2-glycoprotein I of immunoglobulin G (IgG) and/or immunoglobulin M isotype in serum or plasma (in titer greater than 99th percentile for a normal population as defined by the laboratory performing the test), present on two or more occasions, at least 12 weeks apart.

Modified from Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306. [PubMed] [Full Text]

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- In women with APS and a history of stillbirth or recurrent fetal loss but no prior thrombotic history, prophylactic doses of heparin and low-dose aspirin during pregnancy and 6 weeks of postpartum should be considered.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- For women with APS who have had a thrombotic event, most experts recommend prophylactic anticoagulation with heparin throughout pregnancy and 6 weeks postpartum.
- For women with APS who have not had a thrombotic event, expert consensus suggests that clinical surveillance or prophylactic heparin use antepartum in addition to 6 weeks of postpartum anticoagulation may be warranted.
- For long-term management postpartum, patients with APS should be referred to a physician with expertise in treatment of the syndrome, such as an internist, hematologist, or rheumatologist.
- Women with APS should not use estrogen-containing contraceptives.

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Box 2. Clinical Criteria for Diagnosis of Antiphospholipid Syndrome ⇦

1. Vascular thrombosis

   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ, or

2. Pregnancy morbidity

   a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

   b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe preeclampsia, or features consistent with placental insufficiency, or

   c) Three or more unexplained consecutive spontaneous pregnancy losses before the 10th week of pregnancy, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Modified from Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306. [PubMed] [Full Text]

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Summary of Recommendations and Conclusions

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Obstetric indications for antiphospholipid antibody testing should be limited to a history of one fetal loss or three or more recurrent embryonic or fetal losses.
- Testing for antiphospholipid antibodies should be performed in women with a prior unexplained venous thromboembolism, a new venous thromboembolism during pregnancy, or in those with a history of venous thromboembolism but not tested previously.

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Ευχαριστώ πολύ!