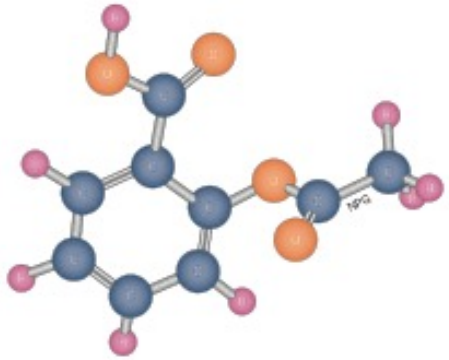


47èmes JOURNÉES NATIONALES
SOCIÉTÉ FRANÇAISE
DE MÉDECINE PÉRINATALE

LYON 18-20 OCTOBRE 2017

Etude ASPRE

VASSILIS TSATSARIS

SFMP 2017, LYON

UNIVERSITÉ PARIS DESCARTES
USPC Université Sorbonne Paris Cité
HÔPITAUX UNIVERSITAIRES PARIS CENTRE
Cochin • Port-Royal • Tarnier • Broca
La Collégiale • La Rochefoucauld • Hôtel-Dieu
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

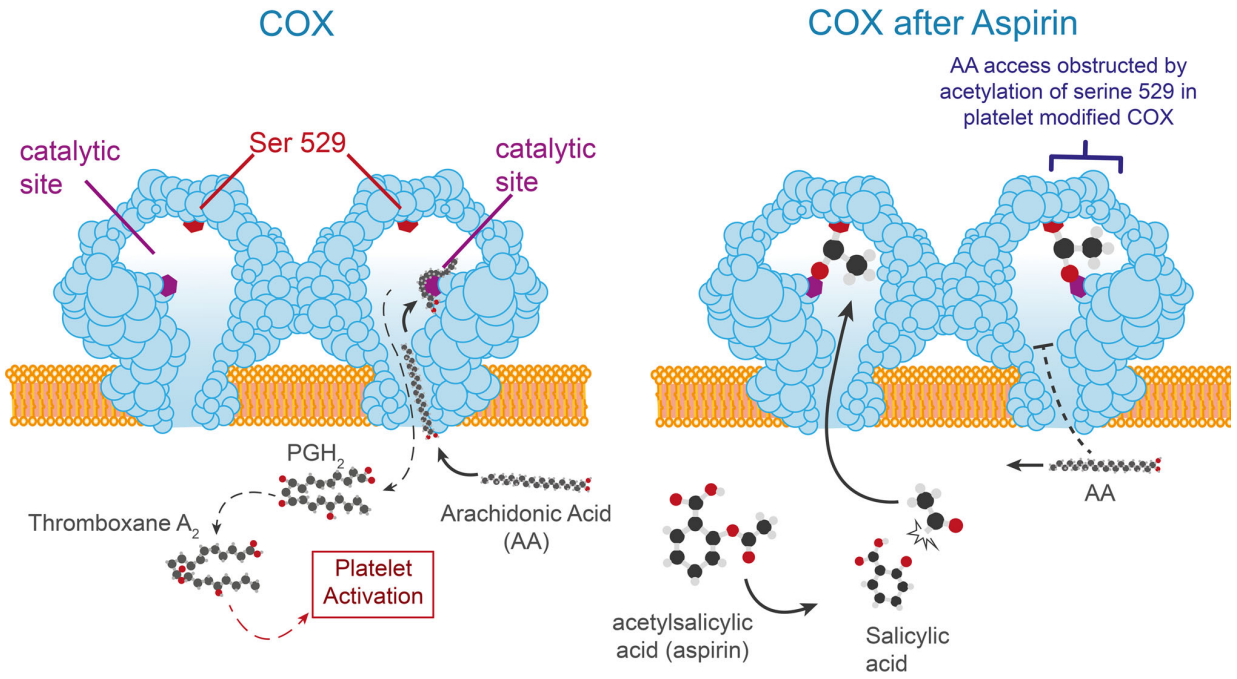
Lien d’intérêts

- Ferring
- Roche diagnostic
- Obseva
- Alexion

Historique de l'aspirine

- Hippocrate (vers 460 av JC) conseillait une tisane de feuilles de saule blanc (salix alba), pour soulager les douleurs et les fièvres.
- 1829 : Pierre-Joseph Leroux, obtient des cristaux solubles après avoir fait bouillir de la poudre d'écorce de saule blanc (la salicyline)
- 1853 : synthèse de l'acide acétylsalicylique (Charles-Frédéric Gerhardt)
- 1971 : découverte du mode d'action : inhibition de la synthèse de prostaglandines par la COX (John Vane, Prix Nobel 1982)

Mode d'action de l'aspirine



- Puissant effet inhibiteur de l'agrégation plaquettaire
- Action rapide < 30min
- Blocage du tunnel en acétylant de façon irréversible une sérine
- Effets sur les plaquettes
  - 5 à 100mg d'aspirine : inhibition dose dépendante de la COX
  - 100mg d'aspirine : inhibition quasi complète de la production de thromboxane A2

Atallah, Drugs, 2017

Etude princeps

PREVENTION OF PRE-ECLAMPSIA BY EARLY ANTIPLATELET THERAPY

M. BEAUFILS, S. UZAN, R. DONSIMONI, J. C. COLAU

Service de Néphrologie, Service de Gynécologie-Obstétrique, and Service central de Biochimie, Hôpital Tenon, Paris, France

THE LANCET, APRIL 13, 1985

TABLE II—OUTCOME OF PREGNANCY

	Group A (n=48)	Group B (n=45)	p
Normal pregnancy	29	12	<0·005
Hypertension (isolated)	19	22	NS
Pre-eclampsia	0	6	<0·01
Fetal and neonatal loss	0	5	<0·02
Severe IUGR (live births)	0	4	<0·05

- Inclusions dès le premier trimestre
- Aspirine 150mg/j + dypiridamole 300mg/j
- De 12 SA à l'accouchement

TABLE I—AGE, PARITY, AND OBSTETRIC HISTORY

	Group A (n=52)	Group B (n=50)
Age (yr, mean ±SD)	28·17±4·8	27·94±4·7
Number with parity:		
1	3	0
2	20	21
3	15	16
⩾4	14	13
Number with known HT	15	19
*Number of following complications**		
Stillbirths	42 *(32)*	31 *(27)*
IUGR	10 *(9)*	12 *(12)*
Spont abortions	20 *(13)*	27 *(21)*
Number with:		
0 complications	14	15
1 complications	29	27
2 complications	5	8
⩾3 complications	4	0

*Given as number of events, with number of patients in parentheses.

*Given as number of events, with number of patients in parentheses.

Indications de l'aspirine

Aspirine Indiquée

- ATCD de prééclampsie
- ATCD de RCIU vasculaire <34 SA
- ATCD de MFIU vasculaire
- Lupus
- SAPL
- ATCD AVC

Aspirine Non Indiquée

- Doppler utérin pathologique
- Dépistage combiné au premier trimestre
- HTA essentielle
- Diabète (DNID, DID)
- FCS à répétition
- MFIU sans pathologie vasculaire

Dépistage de la prééclampsie

First-Trimester Prediction of Hypertensive Disorders in Pregnancy
Leona C.Y. Poon, Nikos A. Kametas, Nerea Maiz, Ranjit Akolekar and Kypros H. Nicolaides
Hypertension published online Mar 9, 2009;

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association®
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First-Trimester Prediction of Hypertensive Disorders in Pregnancy

Leona C.Y. Poon, Nikos A. Kametas, Nerea Maiz, Ranjit Akolekar and Kypros H. Nicolaides

Hypertension published online Mar 9, 2009;

Y=−8.776+14.177×log uterine artery PI MoM+42.960×log MAP MoM−2.249×log PAPP-A MoM−3.529×log PlGF MoM+0.120×BMI in kg/m^2+(−1.472 if parous with no previous PE or 0 if nulliparous or parous with previous PE; R^2=0.636;

In this study, maternal history, uterine artery PI, MAP, and PAPP-A were recorded in all of the cases in the base-cohort population (n=7797). In addition, maternal serum PlGF was measured in a case-control population of 29 cases with early PE, 98 with late PE, 82 with GH, and 418 controls from pregnancies that did not develop any complications and resulted in the live birth of phenotypically normal neonates. The selection of the specific samples from

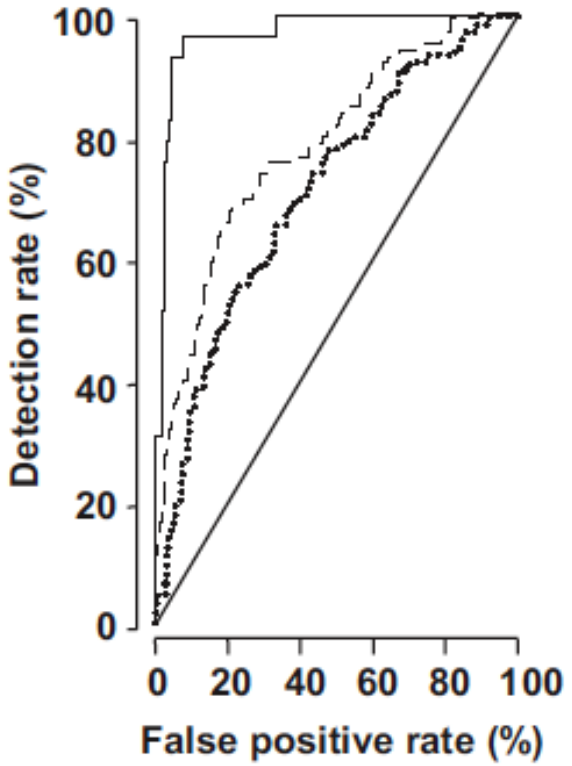


Figure. Detection rates of early PE (solid line), late PE (long-dashed line), and GH (dotted line)

Etude ASPRE

funded by EU FP7 ASPRE project

Combined multimarker screening and randomised patient treatment with aspirin for evidence-based pre-eclampsia prevention.

- Objectif :
  - Etude multicentrique Européenne
  - Dépister au premier trimestre des patientes à haut risque de prééclampsie
    - 11 à 13 SA+6j
    - Age, Taille, Poids, Ethnie, HTA chronique, Lupus ou SAPL, PMA, ATCD de PE, DID ou DNID, Parité, PAM, IP des artères utérines, PAPP-A, PlGF
  - Risque accru de prééclampsie si >1/100 (PE avant 37SA) : 10% des femmes testées
  - Randomisation des patientes à risque de PE avant 37SA : aspirine vs placebo

Etude ASPRE

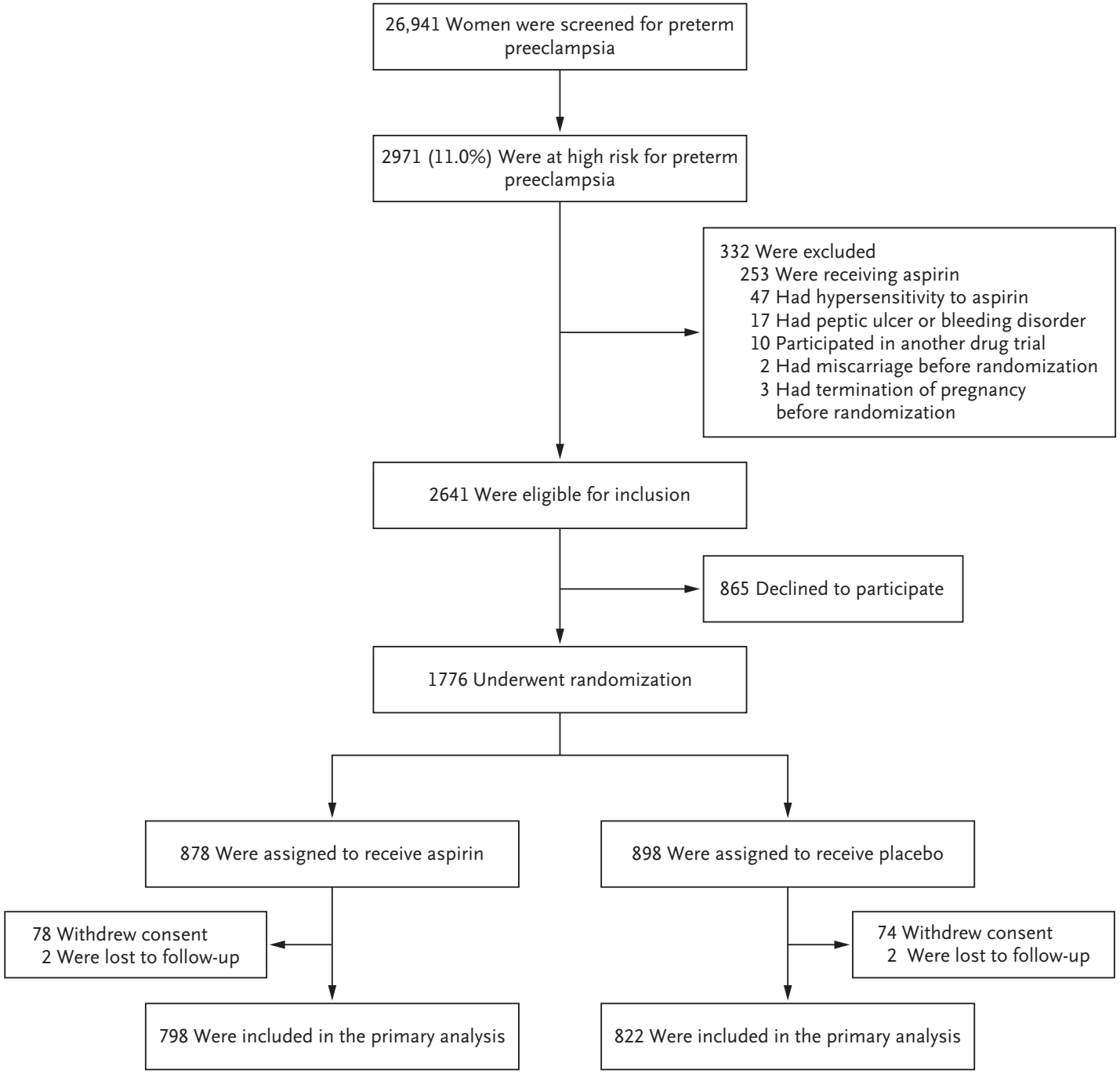
funded by EU FP7
ASPRE
project

- Méthodologie initiale
  - Nécessité d'inclure 33680 patientes qui bénéficieraient d'un dépistage au premier trimestre
  - Pour identifier 3,368 patientes à haut risque qui se verraient proposer une randomisation Aspirine vs placebo
  - L'objectif était de randomiser 1684 patientes.
  - La puissance de l'étude était calculée sur une réduction de 50% de réduction de la survenue d'une prééclampsie

Etude ASPRE

funded by EU FP7
ASPRE
project

- Essai randomisé en double aveugle
- Traitement par aspirine
  - 150 mg/jour le soir
  - De la randomisation jusqu'à 36 SA
- Placebo
  - Comprimé d'aspect analogue à l'aspirine



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Résultats : PE avant 37 SA

funded by EU FP7
ASPRE
project

Table 2. Outcomes According to Trial Group.

Outcome	Aspirin Group (N = 798)	Placebo Group (N = 822)	Odds Ratio (95% or 99% CI)*
Primary outcome: preterm preeclampsia at <37 wk of gestation — no. (%)	13 (1.6)	35 (4.3)	0.38 (0.20–0.74)

Résultats : issues < 34 SA

funded by EU FP7 ASPRE project

Table 2. Outcomes According to Trial Group.

Outcome	Aspirin Group (N = 798)	Placebo Group (N = 822)	Odds Ratio (95% or 99% CI)*
Secondary outcomes according to gestational age			
Adverse outcomes at <34 wk of gestation			
Any — no. (%)	32 (4.0)	53 (6.4)	0.62 (0.34–1.14)
Preeclampsia — no. (%)	3 (0.4)	15 (1.8)	0.18 (0.03–1.03)
Gestational hypertension — no. (%)	2 (0.3)	2 (0.2)	1.02 (0.08–13.49)
Small-for-gestational-age status without preeclampsia — no./total no. (%)†	7/785 (0.9)	14/807 (1.7)	0.53 (0.16–1.77)
Miscarriage or stillbirth without preeclampsia — no. (%)	14 (1.8)	19 (2.3)	0.78 (0.31–1.95)
Abruption without preeclampsia — no. (%)	1 (0.1)	3 (0.4)	0.36 (0.02–7.14)
Spontaneous delivery without preeclampsia — no. (%)	12 (1.5)	12 (1.5)	1.07 (0.37–3.10)

Résultats issues < 37 SA

funded by EU FP7 ASPRE project

Table 2. Outcomes According to Trial Group.

Outcome	Aspirin Group (N = 798)	Placebo Group (N = 822)	Odds Ratio (95% or 99% CI)*
Adverse outcomes at <37 wk of gestation			
Any — no. (%)	79 (9.9)	116 (14.1)	0.69 (0.46–1.03)
Gestational hypertension — no. (%)	8 (1.0)	7 (0.9)	1.19 (0.31–4.56)
Small-for-gestational-age status without preeclampsia — no./total no. (%)†	17/785 (2.2)	18/807 (2.2)	1.01 (0.42–2.46)
Miscarriage or stillbirth without preeclampsia — no. (%)	14 (1.8)	19 (2.3)	0.78 (0.31–1.95)
Abruption without preeclampsia — no. (%)	2 (0.3)	4 (0.5)	0.52 (0.06–4.91)
Spontaneous delivery without preeclampsia — no. (%)	40 (5.0)	49 (6.0)	0.83 (0.47–1.47)

Résultats : issues > 37 SA

funded by EU FP7 ASPRE project

Table 2. Outcomes According to Trial Group.

Outcome	Aspirin Group (N = 798)	Placebo Group (N = 822)	Odds Ratio (95% or 99% CI)*
Adverse outcomes at ≥37 wk of gestation			
Any — no. (%)	178 (22.3)	171 (20.8)	1.12 (0.82–1.54)
Preeclampsia — no. (%)	53 (6.6)	59 (7.2)	0.95 (0.57–1.57)
Gestational hypertension — no. (%)	72 (9.0)	62 (7.5)	1.24 (0.78–1.98)
Small-for-gestational-age status without preeclampsia — no./total no. (%)†	54/785 (6.9)	56/807 (6.9)	1.00 (0.60–1.66)
Stillbirth without preeclampsia — no. (%)	2 (0.3)	2 (0.2)	1.01 (0.08–13.40)
Abruption without preeclampsia — no. (%)	2 (0.3)	2 (0.2)	1.05 (0.08–13.92)

Accouchement avec PE

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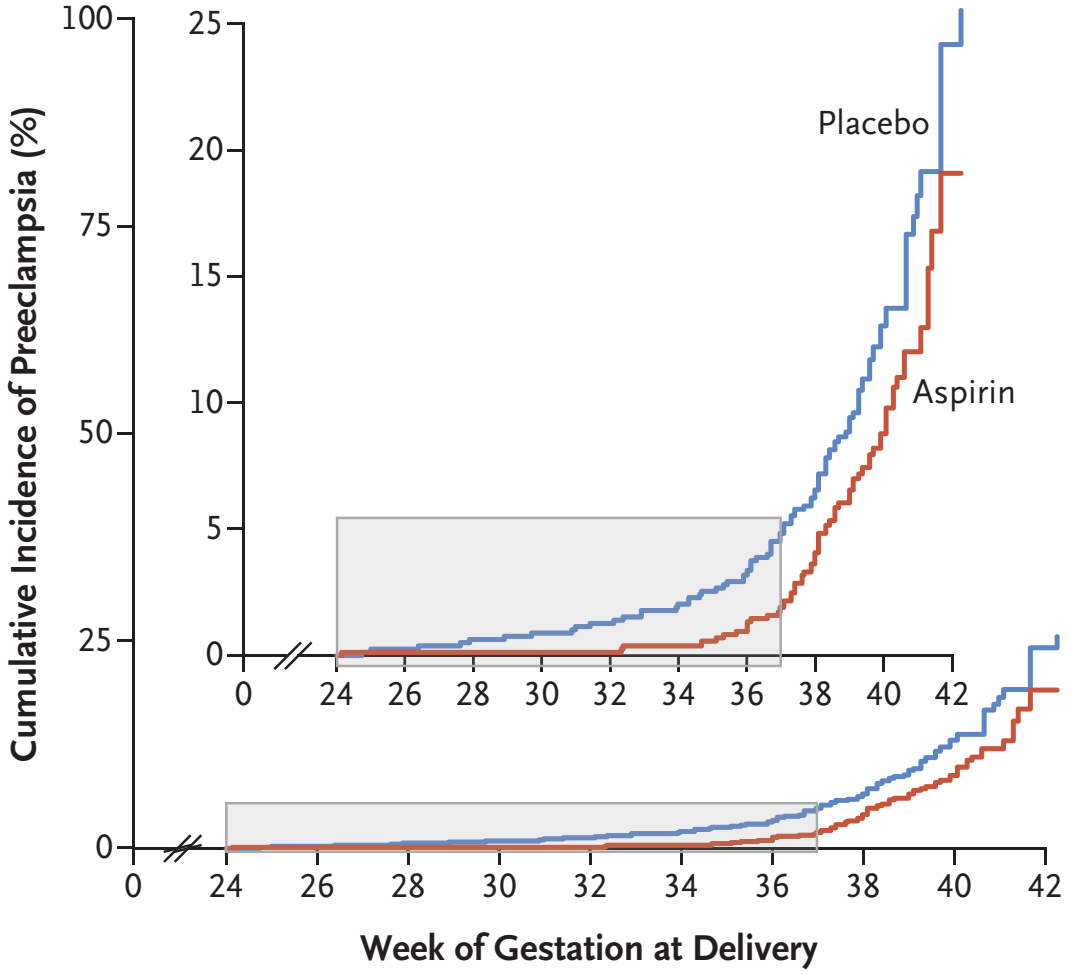

No. at Risk

Placebo	807	802	793	783	775	764	734	619	285	10
Aspirin	785	781	778	776	772	760	740	627	295	12

Issues néonatales

funded by EU FP7 ASPRE project

Outcome	Aspirin Group (N=798)	Placebo Group (N=822)	Odds Ratio (99% CI)
Stillbirth or death — no. (%)			
All stillbirths or deaths	8 (1.0)	14 (1.7)	0.59 (0.19–1.85)
With preeclampsia or status of being small for gestational age	5 (0.6)	8 (1.0)	0.65 (0.15–2.90)
Without preeclampsia or status of being small for gestational age	3 (0.4)	6 (0.7)	0.51 (0.08–3.19)
With placental abruption or bleeding	0	2 (0.2)	0.00 (0.00–∞)
Without placental abruption or bleeding	8 (1.0)	12 (1.5)	0.69 (0.21–2.28)
Death or complications — no. (%)			
Any	32 (4.0)	48 (5.8)	0.69 (0.37–1.27)
Miscarriage, stillbirth, or death	19 (2.4)	26 (3.2)	0.76 (0.35–1.68)
Intraventricular hemorrhage of grade ≥II	2 (0.3)	1 (0.1)	2.23 (0.09–52.70)
Sepsis with confirmed bacteremia in cultures	3 (0.4)	6 (0.7)	0.52 (0.08–3.32)
Anemia resulting in blood transfusion	5 (0.6)	11 (1.3)	0.47 (0.11–1.92)
Respiratory distress syndrome treated with surfactant and ventilation	11 (1.4)	22 (2.7)	0.53 (0.20–1.40)
Necrotizing enterocolitis resulting in surgery	2 (0.3)	1 (0.1)	2.10 (0.09–49.54)
Therapy — no. (%)			
Any	55 (6.9)	60 (7.3)	0.97 (0.58–1.60)
Admission to intensive care unit	48 (6.0)	54 (6.6)	0.93 (0.55–1.59)
Ventilation with positive airway pressure or intubation	37 (4.6)	46 (5.6)	0.85 (0.47–1.52)
Low birth weight — no./total no. (%)*			
<3rd percentile	57/785 (7.3)	63/807 (7.8)	0.92 (0.57–1.51)
<5th percentile	82/785 (10.4)	96/807 (11.9)	0.86 (0.57–1.30)
<10th percentile	148/785 (18.9)	187/807 (23.2)	0.77 (0.56–1.06)

Issues néonatales : RCIU

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project

Outcome	Aspirin Group (N = 798)	Placebo Group (N = 822)	Odds Ratio (99% CI)
Low birth weight — no./total no. (%)*			
<3rd percentile	57/785 (7.3)	63/807 (7.8)	0.92 (0.57–1.51)
<5th percentile	82/785 (10.4)	96/807 (11.9)	0.86 (0.57–1.30)
<10th percentile	148/785 (18.9)	187/807 (23.2)	0.77 (0.56–1.06)

Les sous-groupes

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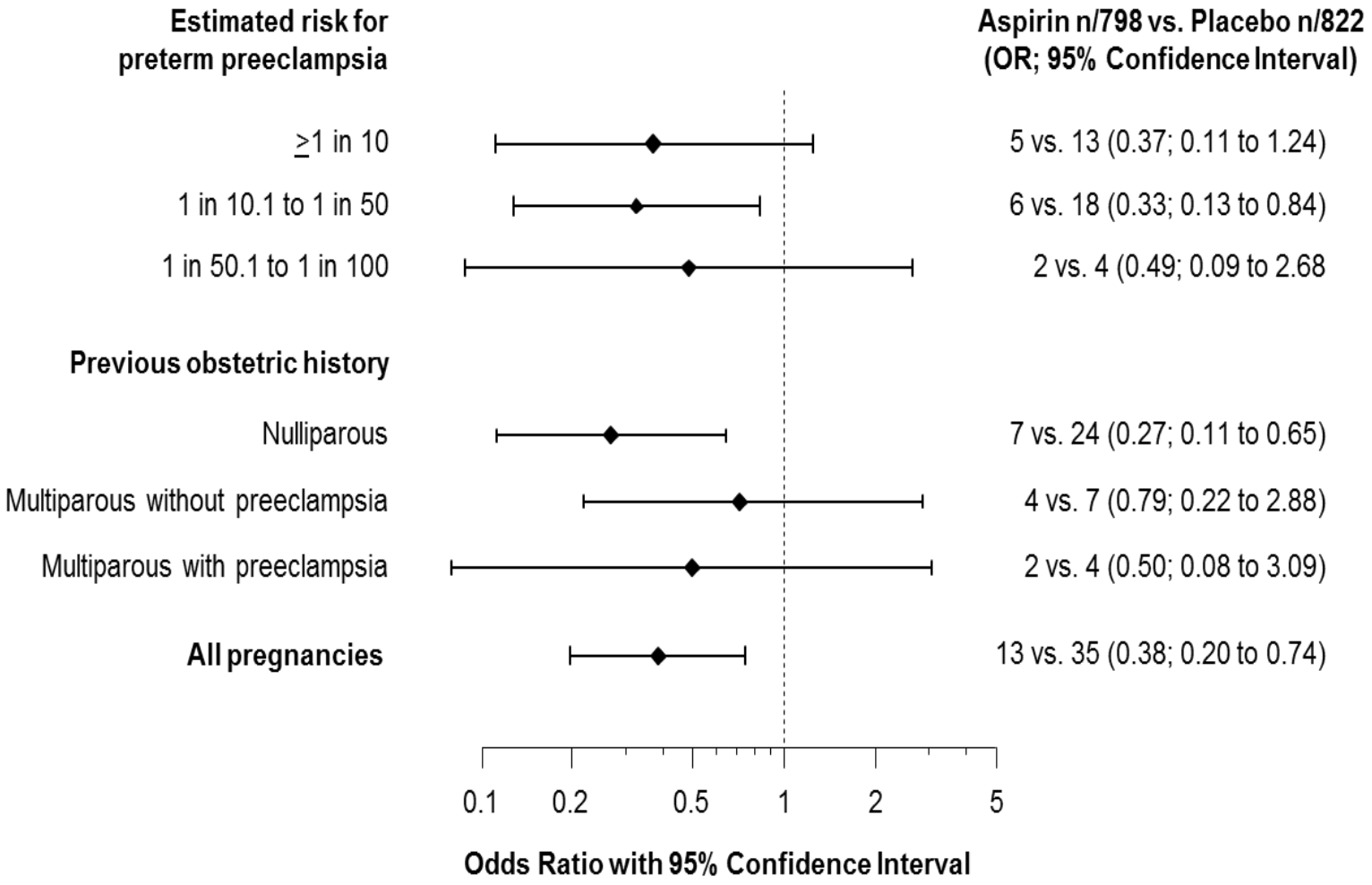

Les sous-groupes

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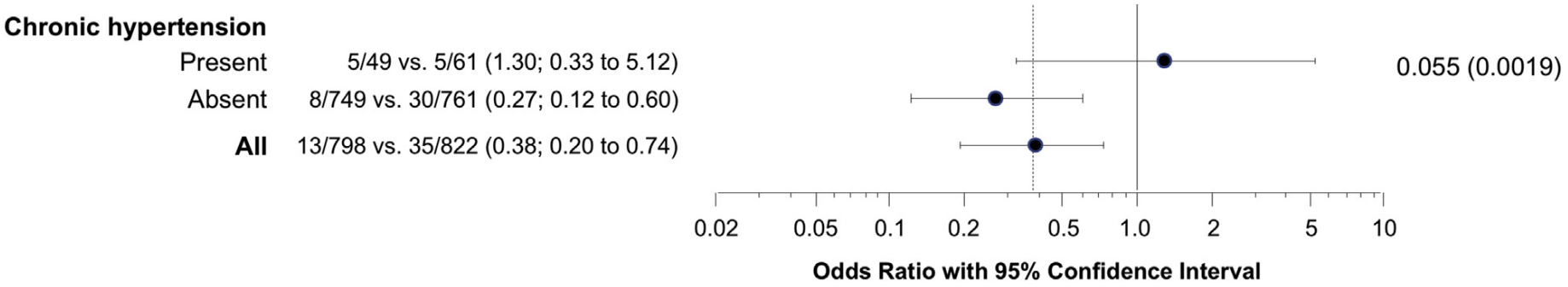
OBSTETRICS

Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history



CONCLUSION: The beneficial effect of aspirin in the prevention of preterm preeclampsia may not apply in pregnancies with chronic hypertension. There was no evidence of heterogeneity in the aspirin effect in subgroups defined according to maternal characteristics and obstetrical history.

Ce que montre cette étude

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project

- L'aspirine à 150 mg/j diminue de 60% le risque de prééclampsie avant 37 SA chez des patientes identifiées à risque de PE après un dépistage T1
- L'aspirine ne diminue pas le risque de RCIU

Ce que cette étude ne montre pas

- ASPRE ne permet pas de conclure à un bénéfice en terme de santé périnatale
- ASPRE ne permet pas de conclure à un intérêt du dépistage précoce de la pré-éclampsie

Pop Totale	PE	PE<37SA
Risque > 1/100	332 (53%)	138 (22%)
Risque < 1/100	298 (47%)	42 (7%)
26941	630	180

- Importance de l'étude SPRE qui compare une stratégie de dépistage FMF vs NICE

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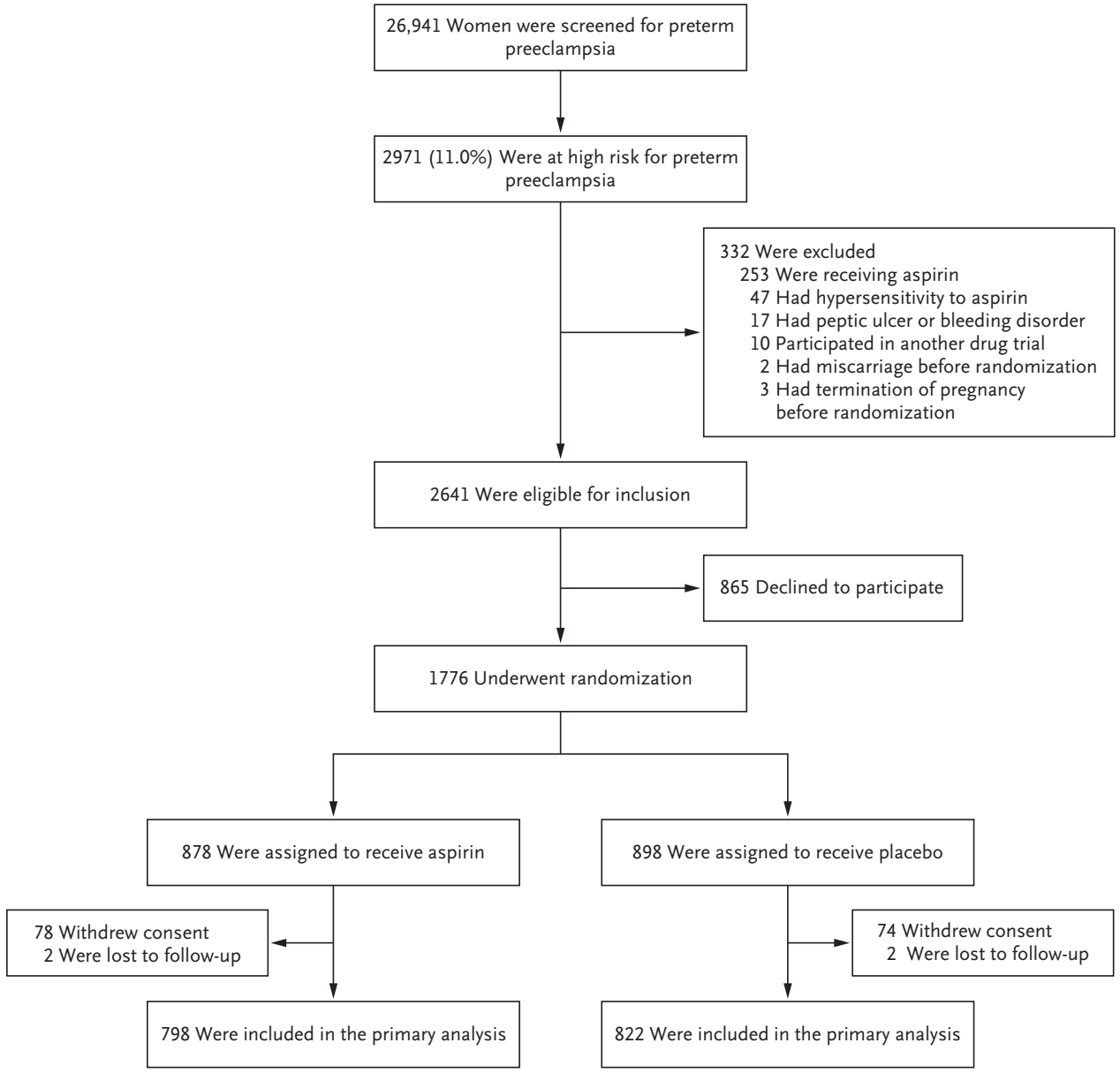
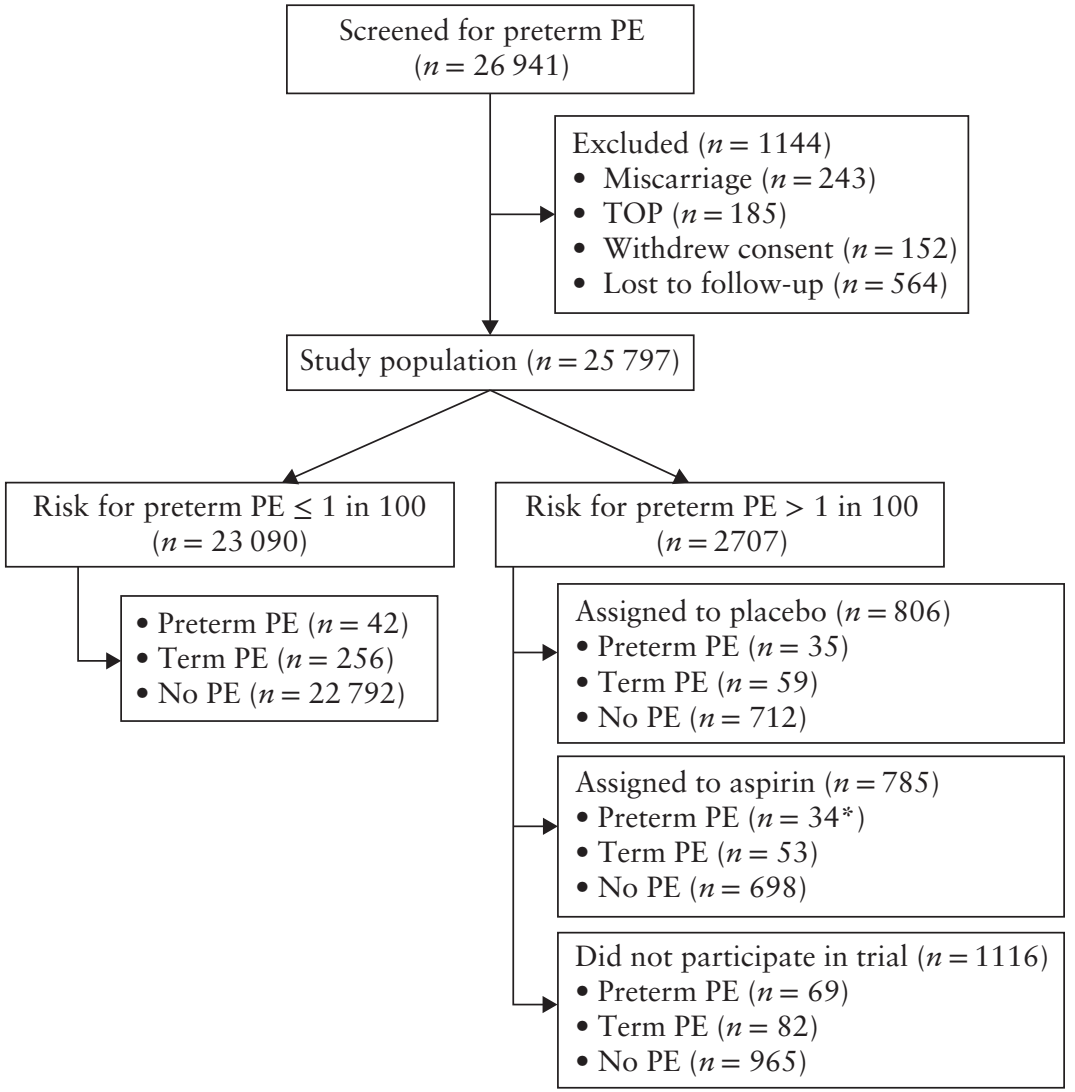
Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia



ASPRE trial: performance of screening for preterm pre-eclampsia



Ultrasound Obstet Gynecol 2017; 50: 492–495

Conclusions

- Dans une population à risque de PE identifiée par un calcul de risque combiné (FMF)
  - L'aspirine diminue de 60% le taux de PE avant 37 SA
  - La réduction du taux de PE avant 34 n'est pas significative (probable manque de puissance)
  - L'aspirine ne diminue pas le risque de RCIU
  - L'aspirine ne diminue pas les indicateurs de morbidité périnatale

- L'étude ASPRE ne démontre pas l'intérêt d'un dépistage de la PE en population générale sur la base de l'algorithme FMF