PRESENTAZIONE

Rapporto OsMed sull'uso dei Farmaci in gravidanza

AIFA - Mercoledì 30 settembre 2020 - Roma

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

12:00 **L'uso dei farmaci in gravidanza: il punto di vista del clinico**

Anna Locatelli, UNIVERSITÀ MILANO BICOCCA

Quale è il problema del clinico

- Pregnant women nowadays are exposed to an average of 2.6 medications

Pre-existing medical conditions

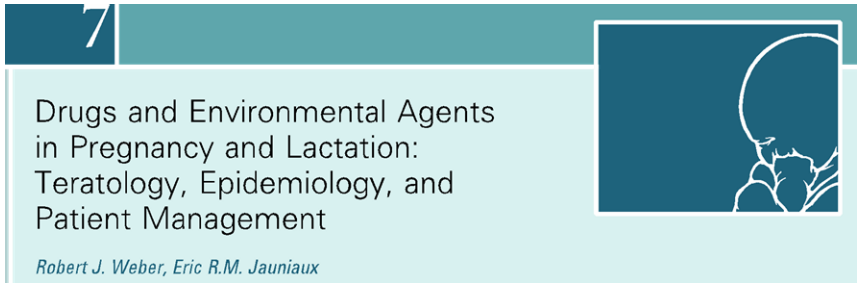
- **Infertility**
- Hypertension
- Diabetes mellitus
- **Depression**
- Seizure disorder
- Endocrine disorders
- Substance abuse
- Autoimmune disorder

Conditions caused by/co-existing in pregnancy

- Nausea and vomiting of pregnancy
- **Preterm labor**
- HDP/preeclampsia
- Gestational Diabetes Mellitus
- **Depression**
- **Infections**
- Pain

- *Starting new drug treatments*: medical problems may occur, or old ones may be exacerbated during pregnancy
- *Adapting the dose* to volume distribution changes throughout the pregnancy

Cosa dovrebbe fare il clinico ?

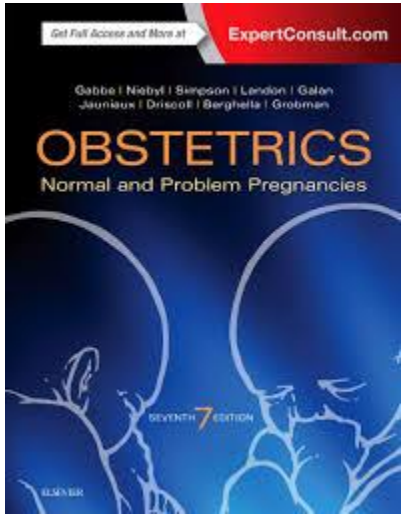


- The assessment of the pregnant patient requiring medication involves a multidisciplinary approach, with **the obstetrician at the center of the decision making and of the communication to the patient**.

- The assessment involves:

1. a thorough physical examination and history with an understanding and prioritizing of various medical conditions that may affect the pregnancy;

2. a complete medication history and reconciliation of the medication regimens to establish current medications (including supplements and over-the-counter products), indications, and the patient's responses to these medications.



Cosa dovrebbe fare il clinico ?

3. evaluation of all evidence related to the effects on the fetus;

4. an open discussion with the patient on her current attitudes toward taking her medications during pregnancy along with their inherent risks;

5. determining medications to be continued during pregnancy with a clear description comparing benefits to the patient and risks to the fetus;

6. developing an ongoing monitoring plan to assess the efficacy of medications during pregnancy and evaluate the effects on the fetus.

- A variety of health care professionals can collect and analyze these informations and provide a team recommendation to the obstetrician.

Table 1 – Effects of pregnancy on Phase I and Phase II drug metabolizing enzymes.

PHASE I Drug Metabolizing Enzymes

Enzyme	Change in Activity	Medications Evaluated
CYP1A2	Decreases	Caffeine[38,51]
CYP2B6	Increases	Methadone[47,48]
CYP2C9	Increases	Glyburide[20]
		Phenytoin[79]
CYP2C19	Decreases (Effect of phenotype unknown)	Proguanil[54,55]
CYP2D6	UM and EM: Increases	Dextromethorphan O-demethylation[38,43]
	IM: No Change	Metoprolol[80]
	PM: Decreases	Paroxetine[44]
CYP3A4/5	Increases	Midazolam[14]
		Nifedipine[39,40]
		Cortisol[81]
		Dextromethorphan N-demethylation[38]

PHASE II Drug Metabolizing Enzymes

Enzyme	Change in Activity	Medications Evaluated
UGT1A1	Increases	Labetalol[67,68]
UGT1A4	Increases	Lamotrigine[61,63,64,66,82–86]
N-acetyltransferase	Minimal decrease, not clinically significant	Caffeine[87]
		Hydralyzine[88]

UM: ultra-rapid metabolizers, EM: extensive metabolizers; IM: intermediate metabolizers; PM: poor metabolizers.

Fig. male Rubi ...d ratio; *F:M*, female/ ...ro N, Moushaev S, ...rm Res. 2018;35:73.)

Farmaci e "barriera placentare"

- Importance of efflux pumps to drug distribution in the placenta
  - they transport substrates from the intracellular to the extracellular compartment
  - **P-glycoprotein** has been detected in human trophoblasts

- Current hypothesis : placental P-glycoprotein protects the developing embryo and fetus from toxic substances and suppresses teratogenesis

Risorse per i clinici

- **REPROTOX** an online database of summaries regarding drugs and known toxic effects, which is owned by a non-profit foundation
www.reprotox.org

- **LactMed** peer reviewed, free database that is maintained by the National Library of Medicine and updated monthly
http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

- **MotherToBaby** evidence based info on medications, pregnancy registries, ongoing studies, maintained by the Organization of Teratology
www.mothertobaby.org

- **Centro antiveleni e tossicologia** c/o Bergamo

- **Treating for Two initiative** of the **CDC** aims to improve both the evidence base and guidance for safer medication use in pregnancy to inform decision making
https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html

- **National Institute of Child Health and Human Development** aims to improve the understanding of obstetric PK and PD through pre-clinical and clinical studies
https://www.nlm.nih.gov/toxnet/index.html

Antidepressivi e gravidanza

Journal of Psychiatric Research 124 (2020) 99–108

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Use of antidepressants during pregnancy and neonatal outcomes: An umbrella review of meta-analyses of observational studies

Annalisa Biffi[a,b,*], Anna Cantarutti[a,b], Federico Rea[a,b], Anna Locatelli[c], Rinaldo Zanini[d], Giovanni Corrao[a,b]

Overall, the effects of AD exposure during pregnancy on neonatal outcomes have been extensively studied, but few of the associations are graded as high quality evidence. More prospective studies and large collaborations with comprehensive standardised reporting of analyses are needed.

JAMA Psychiatry | Original Investigation | META-ANALYSIS

Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression

A Systematic Review and Meta-analysis

Alexander Jarde, PhD; Michelle Morais, MD; Dawn Kingston, PhD; Rebecca Giallo, PhD; Glenda M. MacQueen, MD; Lucy Giglia, MD; Joseph Beyene, PhD; Yi Wang, BHSc; Sarah D. McDonald, MD

Rischio di parto pretermine	1.43
Rischio di distress respiratorio alla nascita	1.33
Rischio di malformazioni CV	1.25

Table 2. Results of the Meta-analyses of Our Primary and Secondary Outcomes

Outcomes	No. of Studies	No. of Women Included	Crude OR/MD (95% CI)	*P* Value	I^2, %
Primary outcomes					
PTB, wk					
<37	14	21 048	1.56 (1.25 to 1.94)[a]	<.001[a]	39
<32	No study reported data				
LBW (<2500 g)	8	3262	1.96 (1.24 to 3.10)[a]	.004[a]	48
SGA (<10%)	1	4044	1.37 (1.10 to 1.70)[a]	.005[a]	NA
LGA (>90%)	No study reported data				
NICU admission	2	200	1.12 (0.40 to 3.15)	.83	0
Secondary outcomes					
Birth weight					
<3%	No study reported data				
<5%	No study reported data				
>95%	No study reported data				
>97%	No study reported data				
>4000 g	No study reported data				
>4500 g	1	973	0.64 (0.18 to 2.29)	.49	NA
Gestational age, wk	7	12 863	−0.15 (−0.41 to 0.11)	.25	70
Birth weight, g	8	13 030	−109 (−195 to -23)[a]	.01	77

Antidepressivi e gravidanza: ATS Brianza

- Ambulatori dedicati per patologia psichiatrica: 2
- Psicologi consultoriali
- Psicologi connessi ai servizi di maternità
- Rete RIMI
- Importanza ITOSS
- Screening EPDS

Figura 2.14.13. Prevalenza d'uso (%) di antidepressivi per tipologia di utilizzatrice nei trimestri prima, durante e dopo la gravidanza

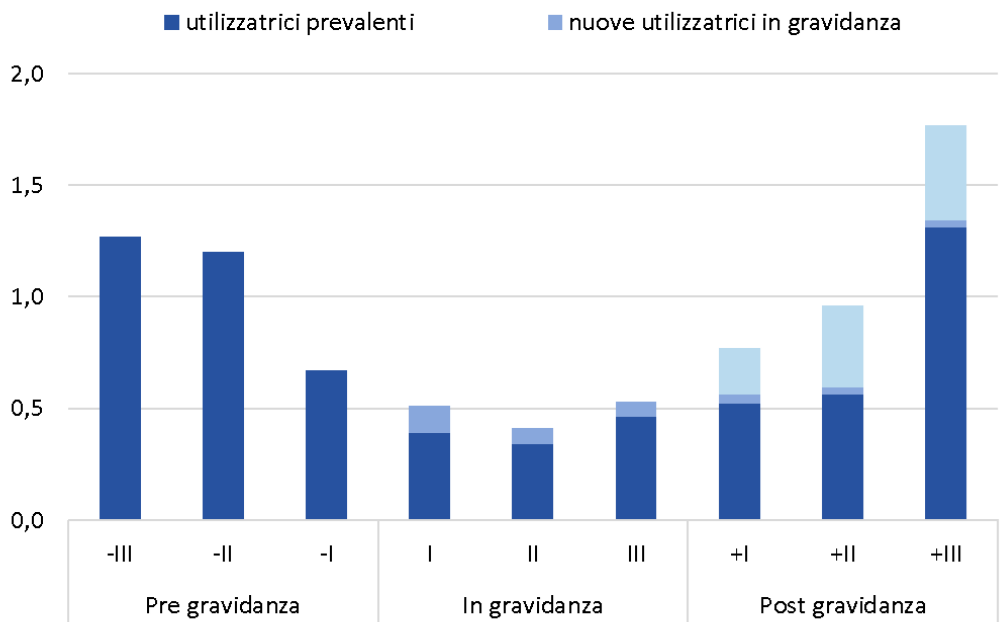


Figura 2.14.1. Prevalenza d'uso di psicofarmaci nei periodi prima, durante e dopo la gravidanza

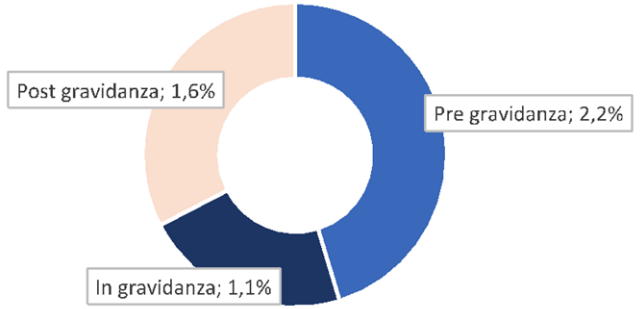
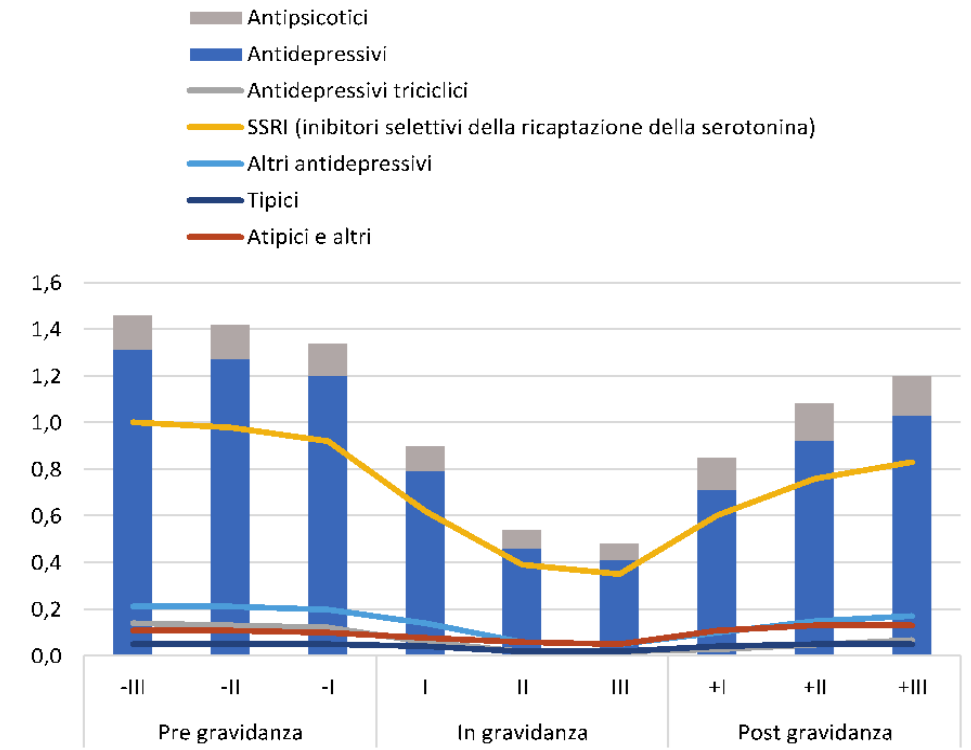


Figura 2.14.2. Prevalenza d'uso (%) di psicofarmaci nei trimestri prima, durante e dopo la gravidanza



Antibiotici e gravidanza

Review Article

Common Bacterial and Viral Infections: Review of Management in the Pregnant Patient

Annals of Pharmacotherapy
2019, Vol. 53(6) 639–651

DOI: 10.1177/1060028018817935
journals.sagepub.com/home/aop
SAGE

Figura 3.16.1. Variabilità regionale della prevalenza d'uso (%) di preparazioni antianemiche, progestinici e antibiotici in gravidanza

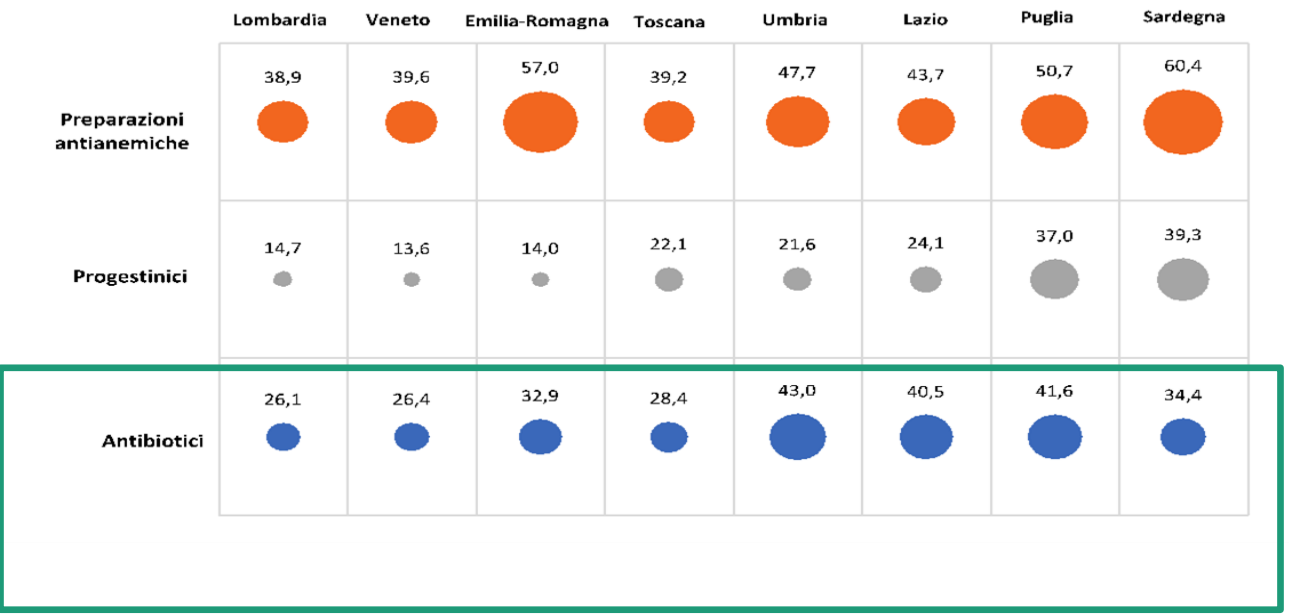
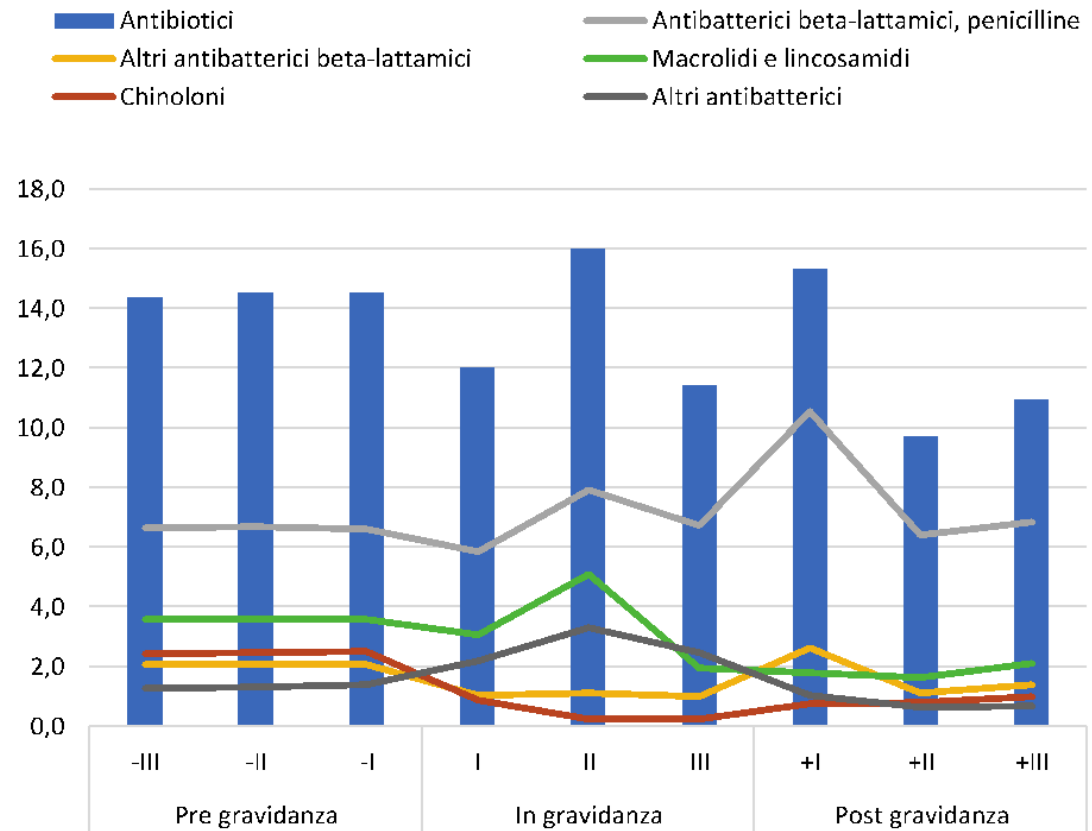


Figura 2.6.2. Prevalenza d'uso (%) di antibiotici per uso sistemico nei trimestri prima, durante e dopo la gravidanza*



** Sono escluse le categorie di farmaci con prevalenza d'uso in gravidanza inferiore all' 1%.*

1. Heikkila AM. Antibiotics in pregnancy–a prospective cohort study on the policy of antibiotic prescription. Ann Med 1993;5:467–71.
2. Harbison AF, Polly DM, Musselman ME. Antiinfective therapy for pregnant or lactating patients in the emergency department. Am J Health Syst Pharm 2015;3:189–97.
3. Lamont HF, Blogg HJ, Lamont RF. Safety of antimicrobial treatment during pregnancy: a current review of resistance, immunomodulation and teratogenicity. Expert Opin Drug Saf 2014;12:1569–81.
4. Miller J.E., Wu C., Pedersen L. H., et al. Maternal antibiotic exposure during pregnancy and hospitalization with infection in offspring: a population–based cohort study. International Journal of Epidemiology. 2018; 47(2); 561–57
5. Broe A, Pottegard A, Lamont RF, et al. Increasing use of antibiotics in pregnancy during the period 2000–2010 prevalence, timing, category, and demographics. BJOG 2014; DOI: 10.1111/1471-0528.12806
6. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. Obstet Gynecol 2006;107:1120–38
7. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. Front Pharmacol 2014;65:1–5.
8. Dunn A.B., Jordan S., Baker B.J., and Carlson N.S. The maternal infant microbiome Considerations for Labor and Birth. Wolters Kluwer Health. 2017; 42(6); 318–325
9. Chernikova DA, Koestler DC, Hoen AG, et al. Fetal exposures and perinatal influences on the stool microbiota of premature infants. J Matern Fetal Neonatal Med. 2016;29(1):99–105.
10. Amir A. Kuperman, Omry Koren. Antibiotic use during pregnancy: how bad is it? BMC Med. 2016; 14:91

Antibiotici e gravidanza

A. common infections: **urinary tract** and **upper respiratory tract**

B. Untreated infections → increased prematurity and low birth weight (antibiotics account for 39% of all dispensed drugs during pregnancy)

C. Several antibiotics are known to cross the placenta

D. Changing of **maternal microbiome** may affect maternal **immune system** and conveying **modified bacterial flora to the fetus**

E. Concerns about implications of antibiotics use on adverse neonatal outcomes

F. Limited evidence on safety and efficacy of antimicrobials

14 RCTs, 7800 donne con parto pretermine in assenza di segni clinici di infezione, 6000 casi da Oracle II

Prophylactic antibiotics for inhibiting preterm labour with intact membranes (Review)

Flenady V, Hawley G, Stock OM, Kenyon S, Badawi N

Outcome	Beneficio (RR)	Significatività (95% CI)
Infezione materna	**0.74**	**0.63 - 0.86**
Parto entro 48 ore	1.04	0.89 - 1.23
Parto prima di 36 o 37 settimane	0.98	0.92 - 1.05
Morte perinatale	1.22	0.88 - 1.69
Morte intrauterina	0.73	0.43 - 1.26
Morte neonatale	**1.57**	**1.03 - 2.40**
Morte dopo 28 giorni	1.06	0.68 - 1.67
Distress respiratorio	0.99	0.84 - 1.16
Enterocolite necrotizzante	1.06	0.64 - 1.73
Sepsi neonatale	0.86	0.64 - 1.16
Emorragia intraventricolare	0.76	0.48 - 1.19

Antibiotici e gravidanza

Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial

S Kenyon, K Pike, D R Jones, P Brocklehurst, N Marlow, A Salt, D J Taylor

Lancet 2008; 372: 1319–27

1. Gli antibiotici ***non sono consigliabili*** *nel parto pretermine spontaneo senza segni clinici di infezione*
2. Lieve aumento rischio CP

Journal of Inflammation Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Antibiotics, Inflammation, and Preterm Labor: A Missed Conclusion

This article was published in the following Dove Press journal:
Journal of Inflammation Research

Anna Locatelli

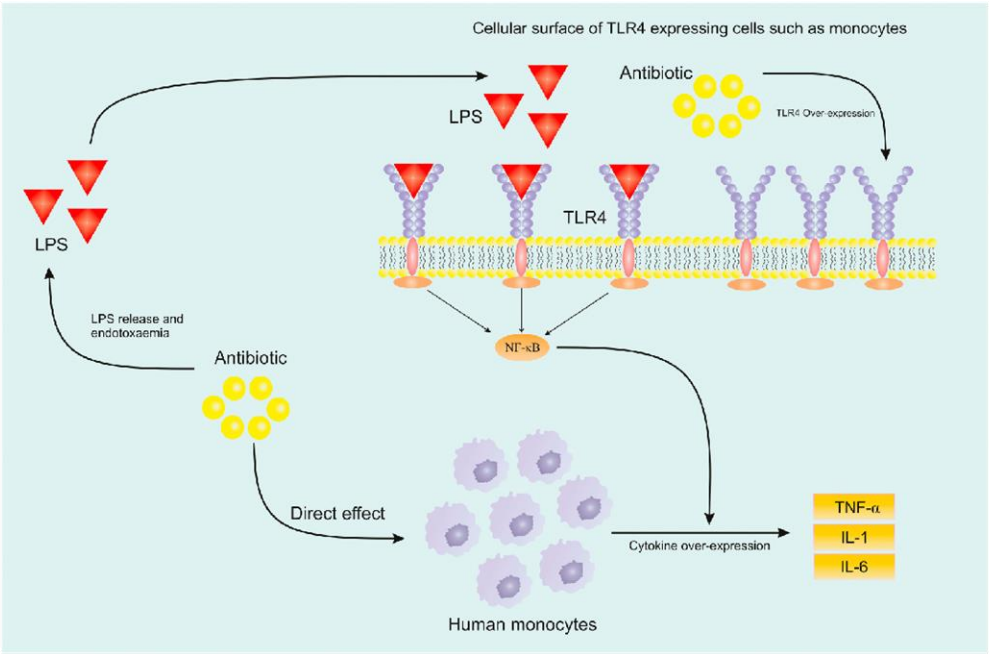


Figure 2 Possible pathways involved in sterile inflammation caused by some antibiotics in the non-infectious situation.
Notes: Modified from *Archives of Medical Research*. Hantoushzadeh S, Norooznezhad AH. Inappropriate Antibiotic Consumption as a Possible Cause of Inflammatory Storm and Septic Shock in Patients Diagnosed with Coronavirus Disease 2019 (COVID-19). Epub 2020 Apr 4. Copyright 2020, with permission from Elsevier.[86]
Abbreviations: IL, interleukin; TNF-α, tumor necrosis factor-α; TLR, Toll-like receptor; LPS, lipopolysaccharide; NF-κB, nuclear factor-κB.

Progestinici e gravidanza

Figura 2.3.1. Prevalenza d'uso di progestinici nei periodi prima, durante e dopo la gravidanza

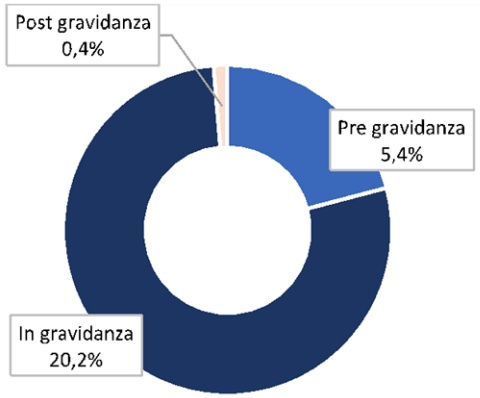
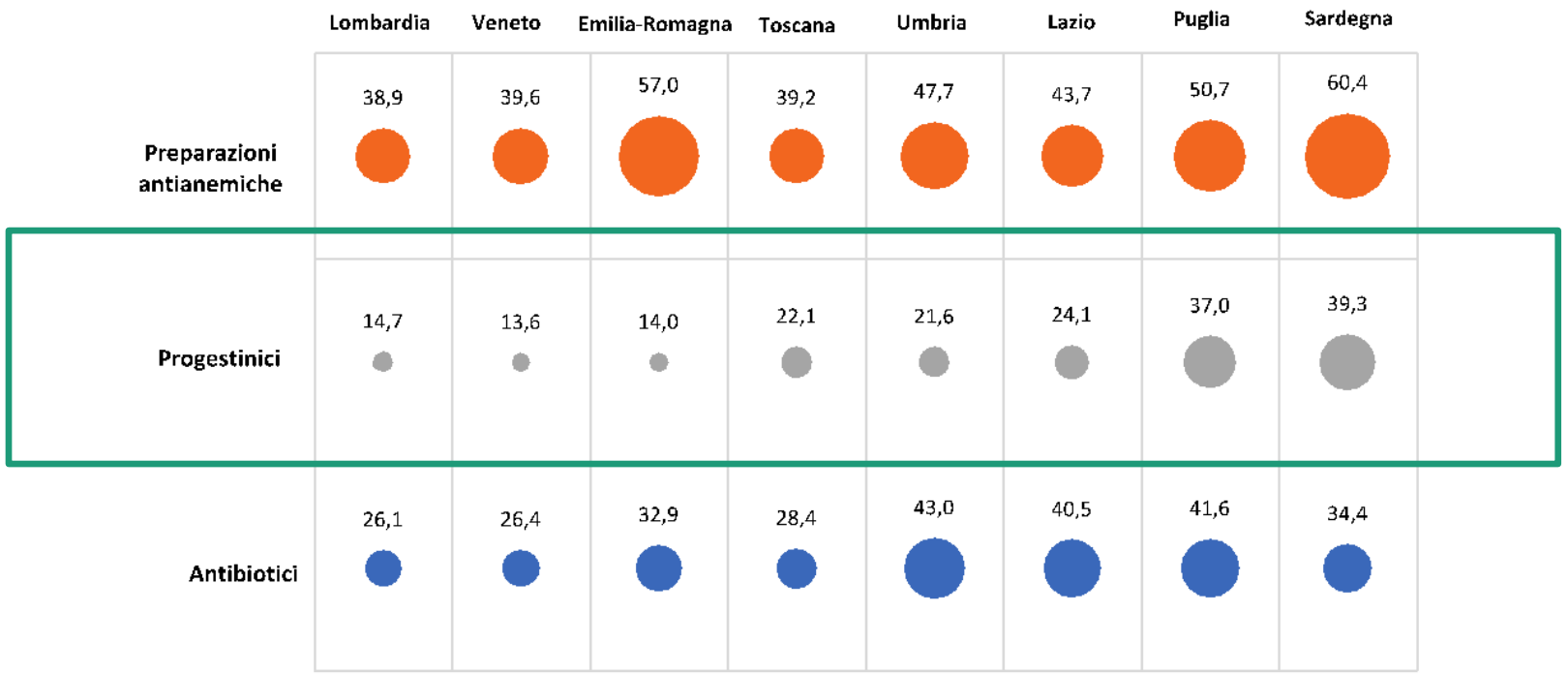


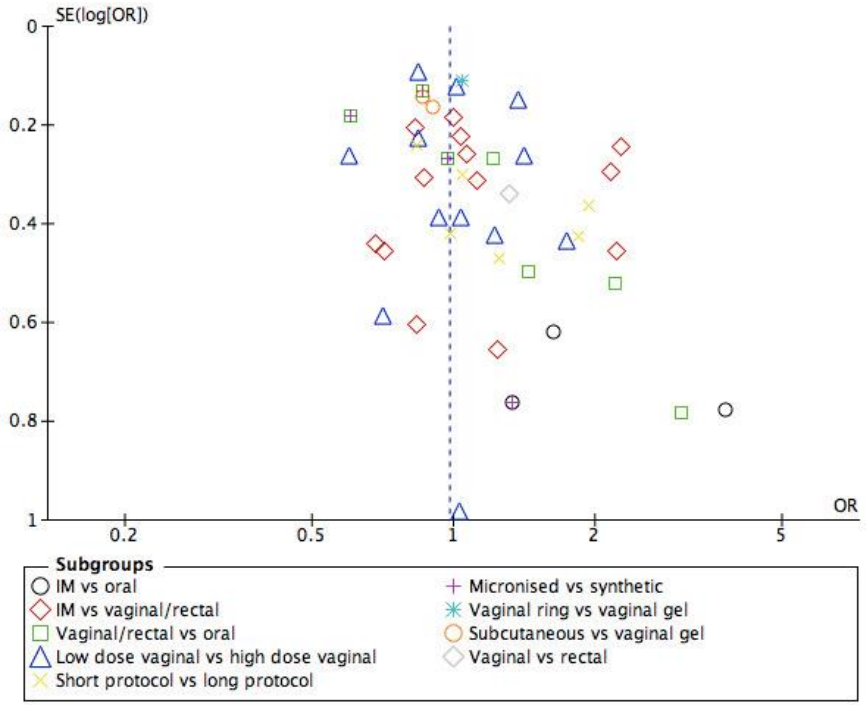
Figura 3.16.1. Variabilità regionale della prevalenza d'uso (%) di preparazioni antianemiche, progestinici e antibiotici in gravidanza



Progestinici e supporto della fase luteale

Cochrane Library

Cochrane Database of Systematic Reviews



Luteal phase support for assisted reproduction cycles (Review)

van der Linden M, Buckingham K, Farquhar C, Kremer JAM, Metwally M

Review: Luteal phase support for assisted reproduction cycles
Comparison: 2 Progesterone vs placebo or no treatment
Outcome: 1 Live birth/ongoing pregnancy rate

Study or subgroup	Progesterone n/N	Placebo/no treatment n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Live birth					
Abate 1999a (1)	15/104	2/52		8.9 %	4.21 [0.93, 19.18]
Subtotal (95% CI)	**104**	**52**		**8.9 %**	**4.21 [0.93, 19.18]**
Total events: 15 (Progesterone), 2 (Placebo/no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.86 (P = 0.063)					
2 Ongoing pregnancy					
Belaisch-Allart 1987 (2)	20/141	16/145		52.8 %	1.33 [0.66, 2.69]
Colwell 1991 (3)	3/15	0/24		1.2 %	13.72 [0.66, 286.96]
Hurd 1996 (4)	4/30	1/26		3.6 %	3.85 [0.40, 36.82]
Kupferminc 1990 (5)	13/54	11/51		33.5 %	1.15 [0.46, 2.87]
Subtotal (95% CI)	**240**	**246**		**91.1 %**	**1.53 [0.91, 2.57]**
Total events: 40 (Progesterone), 28 (Placebo/no treatment)					
Heterogeneity: Chi² = 3.15, df = 3 (P = 0.37); I² =5%					
Test for overall effect: Z = 1.60 (P = 0.11)					
Total (95% CI)	**344**	**298**		**100.0 %**	**1.77 [1.09, 2.86]**
Total events: 55 (Progesterone), 30 (Placebo/no treatment)					
Heterogeneity: Chi² = 4.92, df = 4 (P = 0.30); I² =19%					
Test for overall effect: Z = 2.31 (P = 0.021)					
Test for subgroup differences: Chi² = 1.54, df = 1 (P = 0.21), I² =35%					

0.005 0.1 1 10 200
Favours placebo Favours progesterone

(1) IM progesterone 50 mg daily or vaginal progesterone gel 90 mg daily
(2) Oral dydrogesterone 10 mg 3 times daily. Ongoing pregnancy not further defined
(3) Oral progesterone 200 mg 4 times daily. Ongoing pregnancy not further defined
(4) Vaginal progesterone suppositories 100 mg twice daily + oral E2 2 mg 3 times daily. Ongoing pregnancy not further defined
(5) Oral dydrogesterone 10 mg 3 times daily. Ongoing pregnancy defined as beyond first trimester

Progestinici e gravidanza

FIGURE 5
Miscarriage risk by the number of previous miscarriages

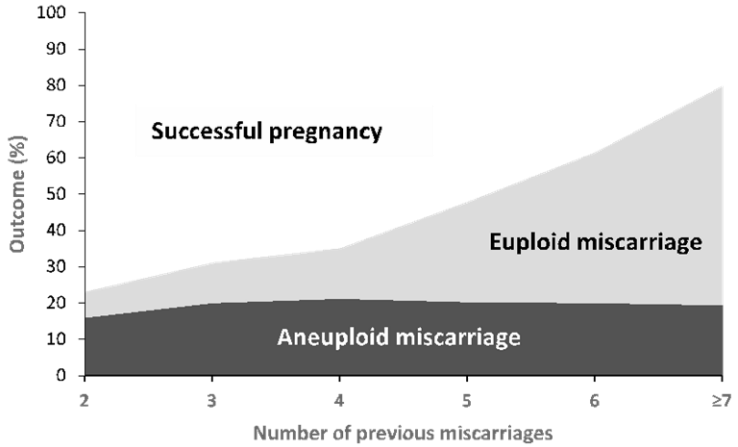
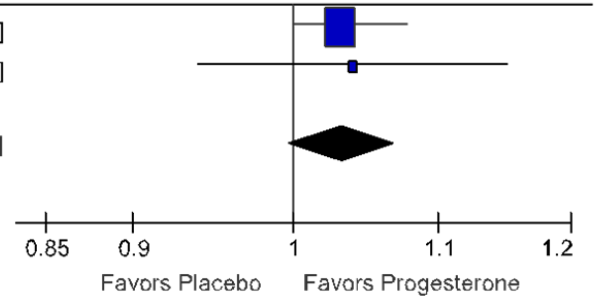


FIGURE 6
Live birth outcome of PROMISE and PRISM trial data

Study or Subgroup	Progesterone Events	Progesterone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PRISM 2019 (a)	1513	2025	1459	2013	84.9%	1.03 [1.00, 1.07]
PROMISE 2015 (b)	262	398	271	428	15.1%	1.04 [0.94, 1.15]
Total (95% CI)		**2423**		**2441**	**100.0%**	**1.03 [1.00, 1.07]**
Total events	1775		1730			

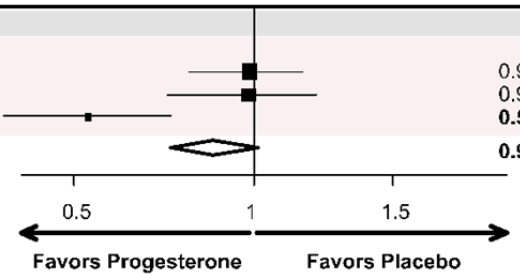
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.78 (P = 0.08)



Footnotes
(a) Live birth after 34 weeks of gestation; adjusted for minimization variables. (b) Live birth after 24 weeks of gestation.
CI, confidence interval; *PRISM*, PRogesterone In Spontaneous Miscarriage; *PROMISE*, PROgesterone in recurrent MIScarriagE.

FIGURE 4
Miscarriage <24 weeks by the number of previous miscarriages

	Progesterone (n/N)	Placebo (n/N)	Risk Ratio [95% CI][1]	% difference	P-value for interaction
Post Hoc Subgroup					
Number of previous miscarriages					
0	229 / 1111	244 / 1127	0.96 (0.82-1.11)	- 1%	
1-2	150 / 777	154 / 738	0.95 (0.78-1.15)	- 1.6%	**0.03**
≥ 3	31 / 137	53 / 148	**0.58 (0.40-0.83)**	**- 13.2%**	
All Participants	**410 / 2025**	**451 / 2013**	**0.91 (0.81-1.01)**	**- 2.6%**	

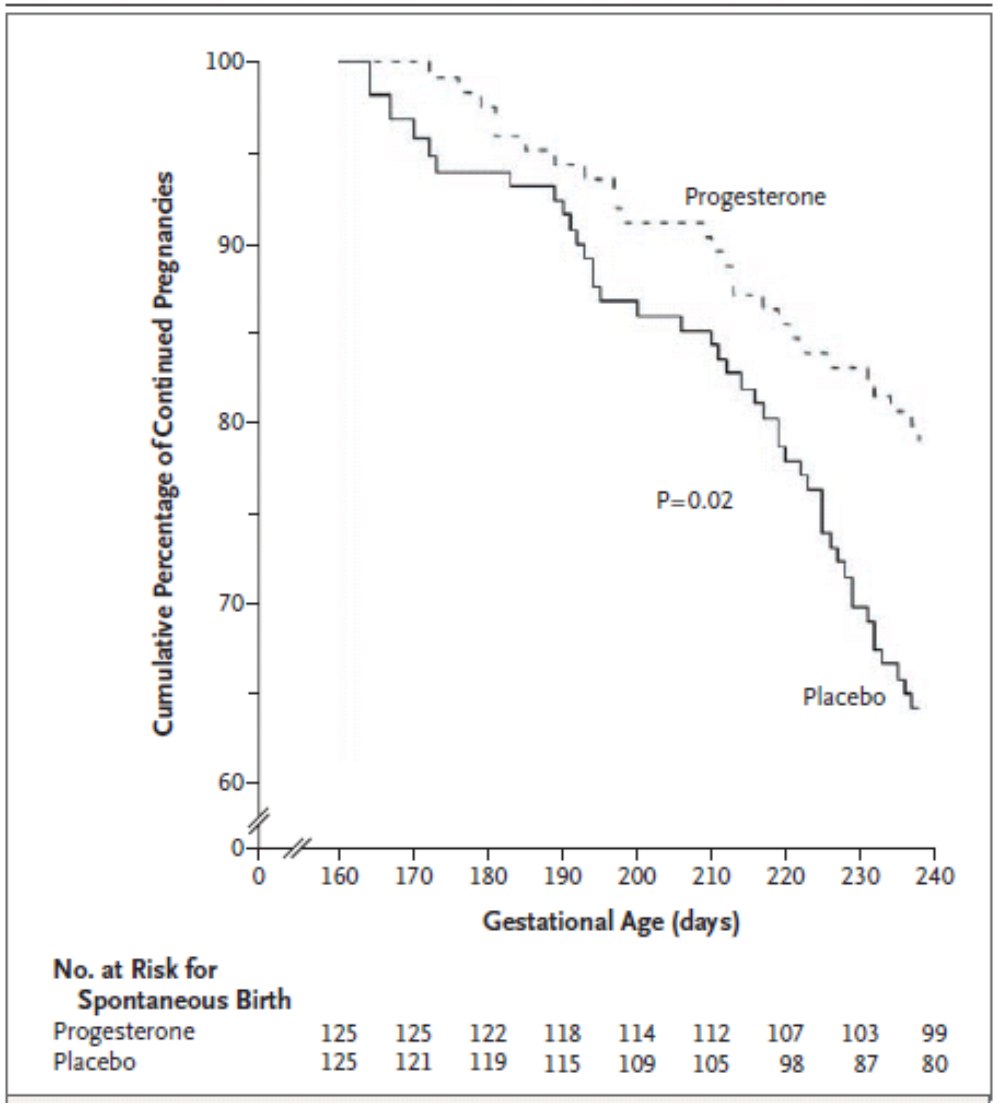


Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence

Check for upd

Arri Coomarasamy, MD, MRCOG; Adam J. Devall, PhD; Jan J. Brosens, PhD; Siobhan Quenby, MD, FRCOG;

Progesterone for sPTD prevention among women with a Short Cervix



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Progesterone and the Risk of Preterm Birth among Women with a Short Cervix

Eduardo B. Fonseca, M.D., Ebru Celik, M.D., Mauro Parra, M.D., Mandeep Singh, M.D., and Kypros H. Nicolaides, M.D., for the Fetal Medicine Foundation Second Trimester Screening Group*

Figure 2. Kaplan–Meier Plot of the Probability of Continued Pregnancy without Delivery among Patients Receiving Vaginal Progesterone as Compared with Placebo.

Progesterone reduces the risk of spontaneous delivery before 34 weeks by 44.2% (hazard ratio for progesterone, 0.57; 95% CI, 0.35 to 0.92; P=0.02). P=0.49 for the test of the proportional-hazards assumption.

Il paradosso della tocolisi in Italia

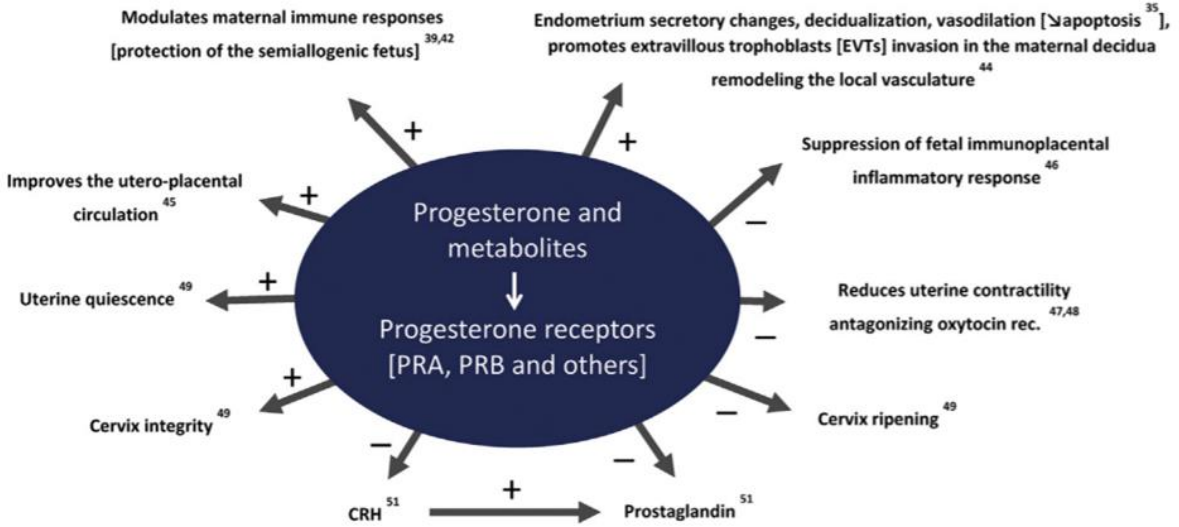


Fig. 2. Pharmacodynamic profile of micronised progesterone [P4] in pregnancy maintenance.

Please cite this article as: Piette PCM, The pharmacodynamics and safety of progesterone, Best Practice & Research Clinical Obstetrics and Gynaecology, https://doi.org/10.1016/j.bpobgyn.2020.06.002

Non tutti i progestinici sono uguali:
P4 o 17hP

Original Research

Progestogens for Maintenance Tocolysis in Women With a Short Cervix

A Randomized Controlled Trial

*Fabio Facchinetti, MD, Patrizia Vergani, MD, Mariarosaria Di Tommaso, MD, PhD, Luca Marozio, MD, PhD, Barbara Acaia, MD, Roberto Vicini, PhD, Lucrezia Pignatti, MD, Anna Locatelli, MD, Marina Spitaleri, MD, Chiara Benedetto, MD, PhD, Barbara Zaina, MD, and Roberto D'Amico, PhD, on behalf of the PROTECT Collaborative Group**

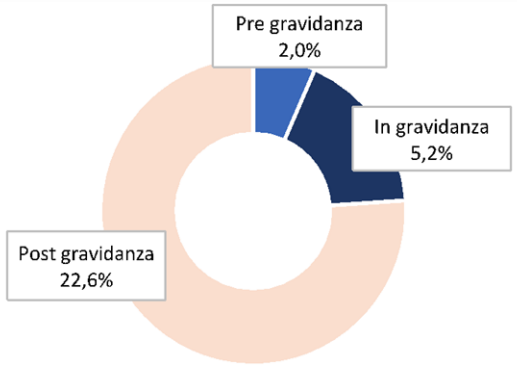
Table 2. Outcomes (N5 235)

Outcome	17a-Hydroxyprogesterone Caproate	Vaginal Progesterone	Control
Primary outcome			
Preterm delivery less than 37 wk of gestation	18/80 (23)	30/78 (39)	17/77 (22)
Secondary outcomes			
Maternal outcomes			
Hospitalized before delivery	10/80 (13)	10/78 (13)	14/77 (18)
GA at delivery	37.76 2.5	36.86 3.4	37.76 2.5
Preterm delivery at less than 35 wk of gestation	7/80 (9)	18/78 (23)	7/77 (9)
Preterm delivery at less than 32 wk of gestation	1/80 (1)	4/78 (5)	3/77 (4)
Neonatal outcomes			
Birth weight (kg	3.066 0.60	2.906 0.66	3.056 0.67
Birth weight less than 2,500 g	14/80 (8)	18/76 (24)	14/76 (18)
Birth weight less than 1,500 g	1/80 (1)	3/76 (4)	0/76 (0)
LGA greater than 90th centile	11/78 (14)	11/72 (15)	14/76 (18)
SGA 10th centile or less	4/78 (5)	2/72 (3)	5/76 (7)
NICU admission	4/80 (5)	13/77 (17)	8/76 (11)
NICU stay (d)	10 (3–18)	12 (9–41)	23 (2–45)
Need of oxygen supply in NICU	1/80 (1)	6/78 (8)	4/77 (5)
Composite morbidity	6/80 (8)	9/78 (12)	7/77 (9)
Congenital anomalies	0/80 (0)	2/78 (3)	3/77 (4)

CI, confidence interval; RR, relative risk; GA, gestational age; MD, mean difference; LGA, large for gestational age; SGA, small for gestational age; NICU, neonatal intensive care unit.
Data are n/N (%), mean6 standard deviation, or median (interquartile range) unless otherwise specified.
* The comparison between NICU stays was performed by Wilcoxon rank-sum test.

Nessuna differenza

Figura 2.5.1. Prevalenza d'uso di eparinici nei periodi prima, durante e dopo la gravidanza



Eparina e gravidanza

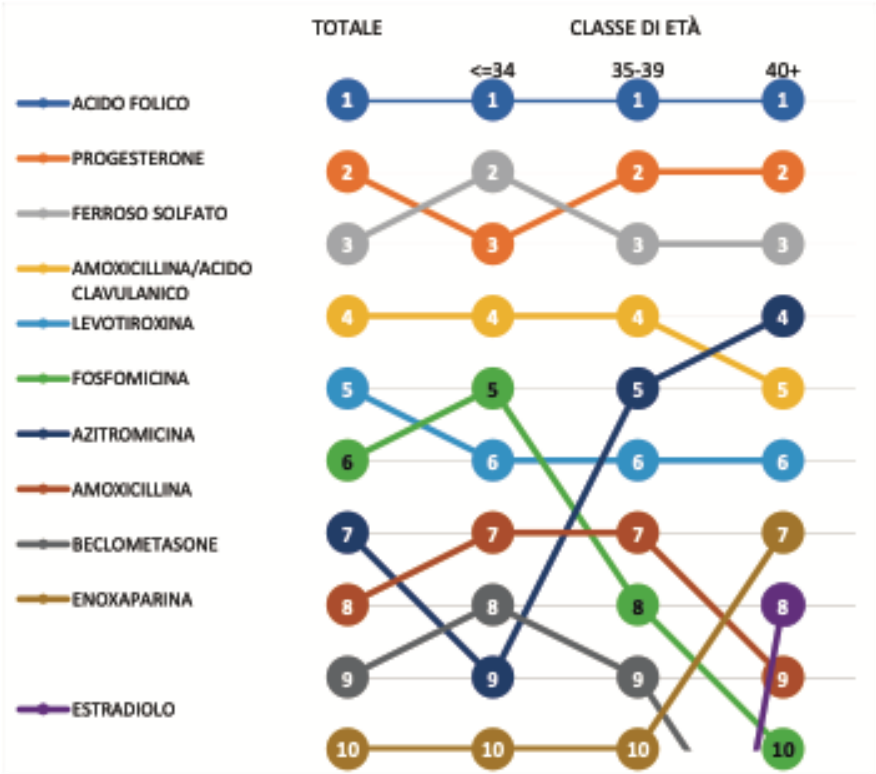
LDA with prophylactic LMWH (usually enoxaparin 40 mg subcutaneously daily) is the standard for pregnancy prophylaxis in women **who meet criteria for OB-APS**

Figura 3.16.2. Variabilità regionale della prevalenza d'uso (%) di farmaci per i disturbi della secrezione acida, eparinici, antinfiammatori e corticosteroidi in gravidanza

	Lombardia	Veneto	Emilia-Romagna	Toscana	Umbria	Lazio	Puglia	Sardegna
Farmaci per i disturbi della secrezione acida	4,8	4,3	7,8	4,8	3,3	6,8	7,2	8,4
Eparinici	2,7	3,0	2,8	6,5	3,0	12,5	6,5	5,3
Antinfiammatori	0,8	0,7	1,2	1,5	1,5	2,7	4,0	3,3
Corticosteroidi	1,9	2,2	2,9	4,8	4,4	8,3	6,6	7,0

Eparina e gravidanza

Figura 1.6. *Ranking* dei primi dieci principi attivi più prescritti in gravidanza *overall* e per classe di età



AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS SYSTEMATIC REVIEW

Efficacy of low-molecular-weight heparin on the outcomes of in vitro fertilization/intracytoplasmic sperm injection pregnancy in non-thrombophilic women: a meta-analysis

XIU-LI YANG[1], FEI CHEN[1], XIU-YING YANG[2], GUAN-HUA DU[2] & YANG XU[1]

[1]Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing, and [2]State Key Laboratory of Bioactive Substance and Function of Natural Medicines and Beijing Key Laboratory of Drug Target and Screening Research, Institute of Materia Medica of Peking Union Medical College, Beijing, China

Eparina e Adverse Pregnancy Outcome

i.e.: A 29-year-old pregnant woman who is heterozygous for the factor V Leiden mutation was referred to your clinic to discuss the potential benefit of low-molecular-weight heparin to prevent future pregnancy complications. She has a history of 6 pregnancy losses (8, 11, 16, 17, 21 and 25 weeks gestation). She has one living child who was delivered at 29 weeks by cesarean section. She has no personal or family history of venous thromboembolism . Testing for antiphospholipid syndrome was negative.

a) *Effect on **trophoblast***:

promote the differentiation and invasion of the trophoblast in vivo

- **Quenby S Ob Gyn 2004, Leach RE Dev Biol 2004**

b) *Effect on **inflammation***:

prevent monocyte adhesion to activated endothelium **Manduteanu B Pharmacology 2007**

inhibit tumor necrosis factor a-induced leukocyte rolling **Wan MX Inflamm Res 2001**

Prevents complement activation **Girardi G Nat Med 2004**

c) *Effect on **perfusion***:

decrease vascular resistance, in vitro and in vivo

Mello Hypertension 2005

Reantragoon S Arch Biochem Biophys 1994

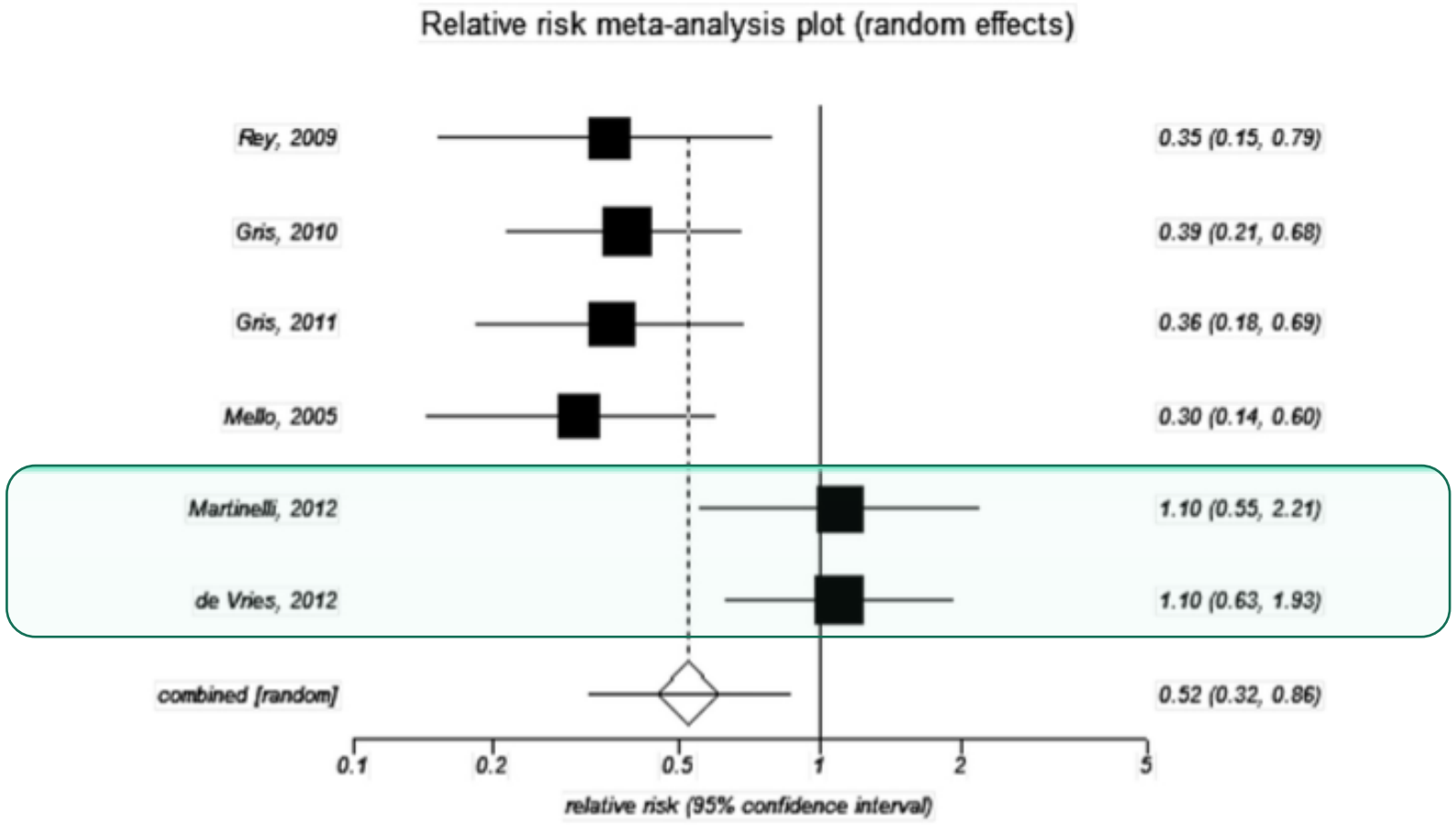
Torricelli M Ultrasound med Biol 2006

Eparina e gravidanza

Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications

Marc A. Rodger,[1-4] Marc Carrier,[1,2,4] Grégoire Le Gal,[1,2,4] Ida Martinelli,[5] Annalisa Perna,[6] Évelyne Rey,[7] J. I. P. de Vries,[8] and Jean-Christophe Gris,[9] on behalf of the Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group

BLOOD 2014



PE (70%ePE), SGA (10°pct), distacco di placenta e MEF>20 sett

(p=0.01).Heterogeneity I2= 69%

Eparina e gravidanza

Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials

*Marc A Rodger, Jean-Christophe Gris, Johanna I P de Vries, Ida Martinelli, Évelyne Rey, Ekkehard Schleussner, Saskia Middeldorp, Risto Kaaja, Nicole J Langlois, Timothy Ramsay, Ranjeeta Mallick, Shannon M Bates, Carolien N H Abheiden, Annalisa Perna, David Petroff, Paulien de Jong, Marion E van Hoorn, P Dick Bezemer, Alain D Mayhew, for the Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group**

Summary

Background Placenta-mediated pregnancy complications include pre-eclampsia, late pregnancy loss, placental

Lancet 2016; 388: 2629–41

Implications of all the available evidence

Daily antepartum low-molecular-weight heparin injections do not seem to reduce the risk of recurrent placenta-mediated pregnancy complications in high-risk patients except in a small subgroup of women with previous abruption. The latter finding should be replicated in future multicentre trials.

Sottopopolazioni che potrebbero giovarne

The NEW ENGLAND JOURNAL of MEDICINE

Farmacologia in gravidanza

Perspective

APRIL 4, 2019

Pharmacologic Research in Pregnant Women — Time to Get It Right

Ahizechukwu C. Eke, M.D., M.P.H., Kelly E. Dooley, M.D., Ph.D., and Jeanne S. Sheffield, M.D.

Drug Trial Designs Suitable for Pregnant Women.

Trial Design	Advantages	Disadvantages
Staggered trial design — Conduct stand-alone phase 1 trials simultaneously with phase 3 trials in the general population.*	Trials will generate phase 1 outcome data in pregnant women; women in later stages of pregnancy can be enrolled before women in the first trimester.	Studies cannot begin until phase 2 trials in the general population are complete.
Embedded trial design — Embed phase 1 trials for pregnant women into late phase 2 or phase 3 trials.*	Researchers can provide pregnancy-specific data sooner than would be possible with stand-alone trials because the subgroup of pregnant women can be given priority in the analysis stage.	Studies are logistically challenging; the availability of data from the overall population can be delayed if pregnant women are enrolled at a slower rate than nonpregnant adults.
Opportunistic study design — Enroll women who become pregnant while taking a drug as part of their clinical care or as part of a study.	Investigators would already be familiar with the study protocol, since they would have participated in earlier research phases with nonpregnant women; start-up costs and monitoring requirements are lower than in other types of trials in pregnant women.	Enrollment is likely to be slower than in other types of trials in pregnant women.

* The options are discussed in detail by Baylis and Halperin.[4]

Prospettive future

1. Favorire team multidisciplinari/esperti che considerino i differenti punti di vista
2. Confronto tra esiti di popolazioni che mostrano uso differente dei farmaci
3. Studi pragmatici specifici per la gravidanza
4. Importanza degli studi osservazionali di coorte population-based per definire i rischi di una popolazione esposta vs non esposta (Canova, Cantarutti *Int. J. Environ. Res. Public Health* **2020**, *17*, 5276; doi:10.3390/ijerph17155276)