FERRARA, 22 MAGGIO 2015

RIDOTTO TEATRO COMUNALE
Cso Martiri della Libertà

LE INFEZIONI DEL BASSO TRATTO UROGENITALE FEMMINILE

INFEZIONI DELLE BASSE VIE URINARIE IN GRAVIDANZA: PROBLEMATICHE MATERNE ED EMBRIO-FETALI

Filomena G. Sileo, Modena
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UNIVERSITÀ DEGLI STUDI
DI MODENA E REGGIO EMILIA

Why urogenital infections are so important in pregnancy?

Ascending genital tract infection as cause of intrauterine infection

Intrauterine infection implicated in

up to 40% of spontaneous preterm birth

Preterm birth

- Prevalence of preterm birth: 5-15% of all pregnancy
  - 2/3 of early infant deaths
  - 60% perinatal mortality and long-term disability
  - Annual cost for USA: at least $26.2 billion per year

- Two major causes:
  - 2/3: spontaneous onset of labour
  - 1/3: medically indicated for maternal or fetal complications

R. L. Goldenberg, J. F. Culhane, J. D. Iams, R. Romero, Lancet 371, 75–84 (2008)
R. Romero, S. K. Dey, S. J Fisher, Science vol 345, issue 6198 (2014)

Preterm labour: not just early onset of labour

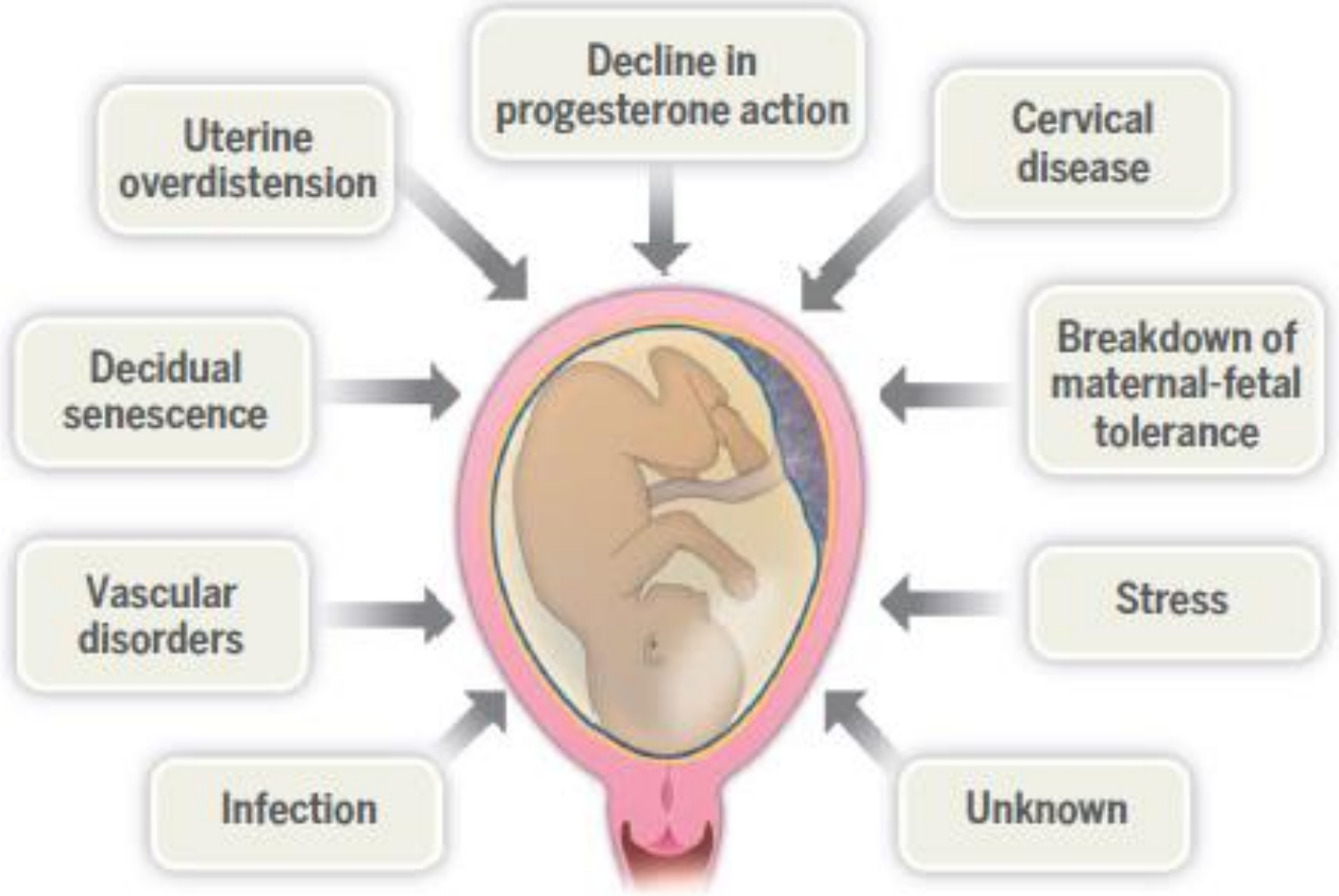
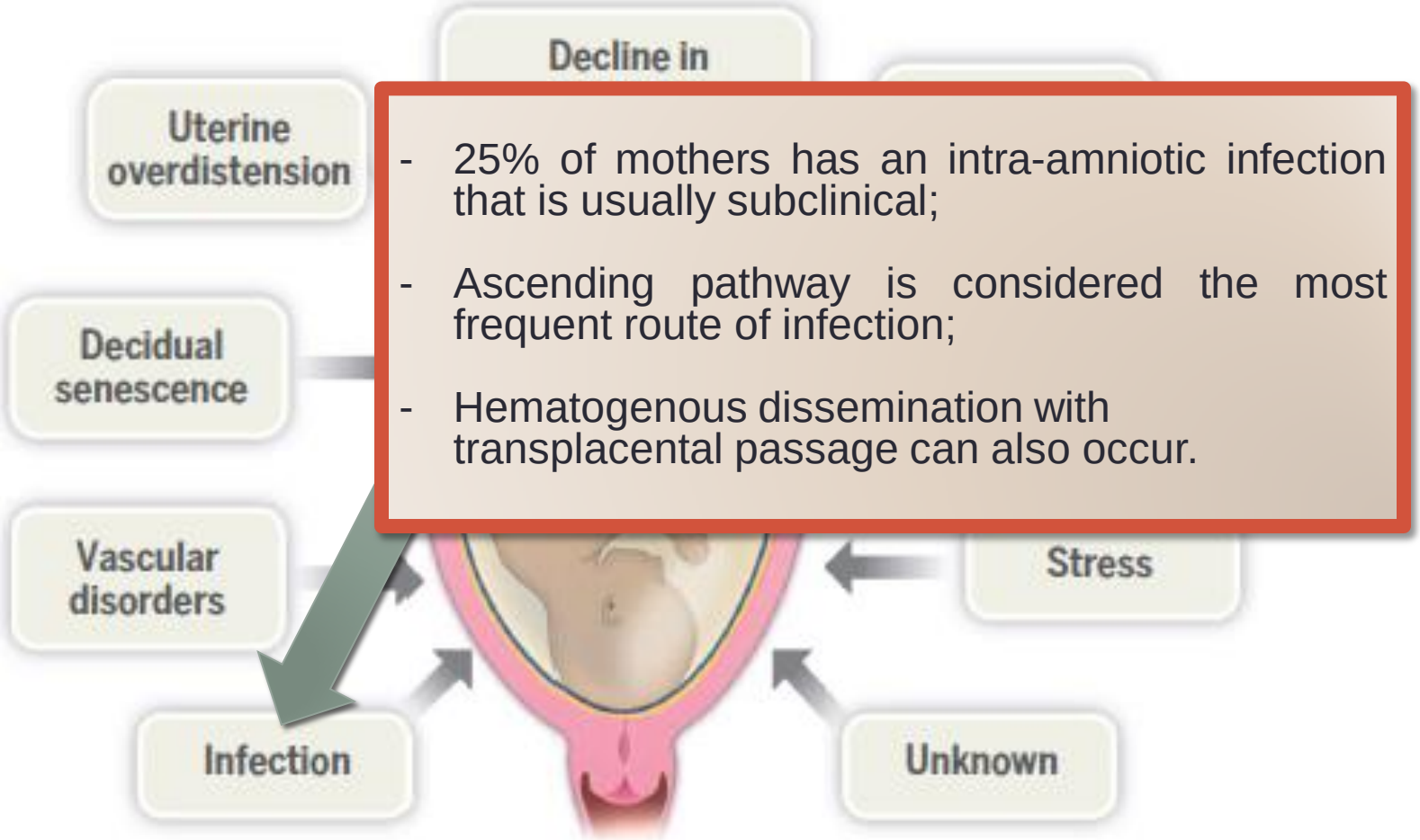


Fig. 2. Proposed mechanisms of disease implicated in spontaneous preterm labor. Genetic and environmental factors are likely contributors to each mechanism.

Preterm labour: one syndrome, many causes. Romero et al. – Science 2014. Aug 15;345(6198):760-5.

Preterm labour: not just early onset of labour



- 25% of mothers has an intra-amniotic infection that is usually subclinical;
- Ascending pathway is considered the most frequent route of infection;
- Hematogenous dissemination with transplacental passage can also occur.

Fig. 2. Proposed mechanisms of disease implicated in spontaneous preterm labor. Genetic and environmental factors are likely contributors to each mechanism.

Preterm labour: one syndrome, many causes. Romero et al. – Science 2014. Aug 15;345(6198):760-5.

Microbial-induced inflammation

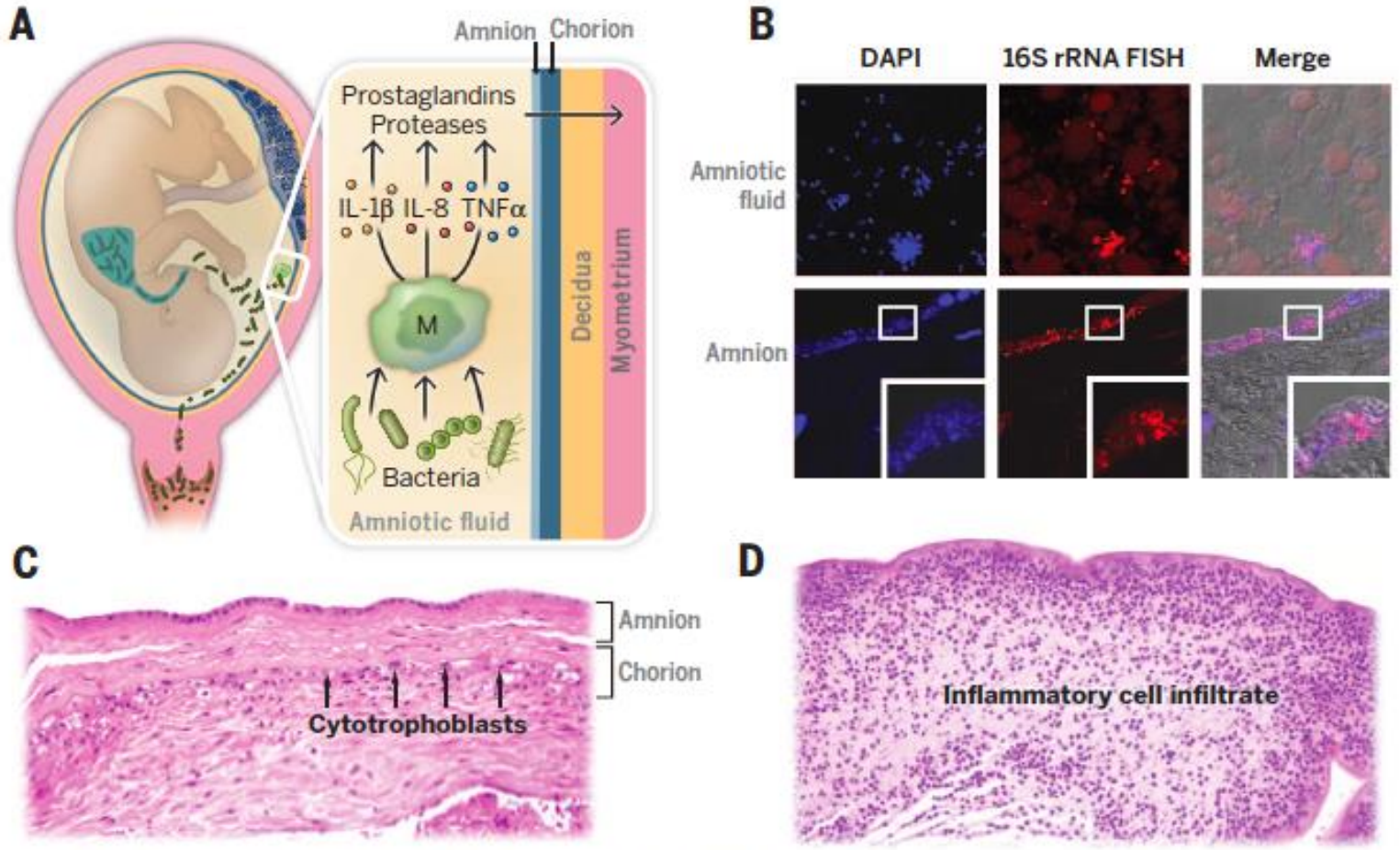
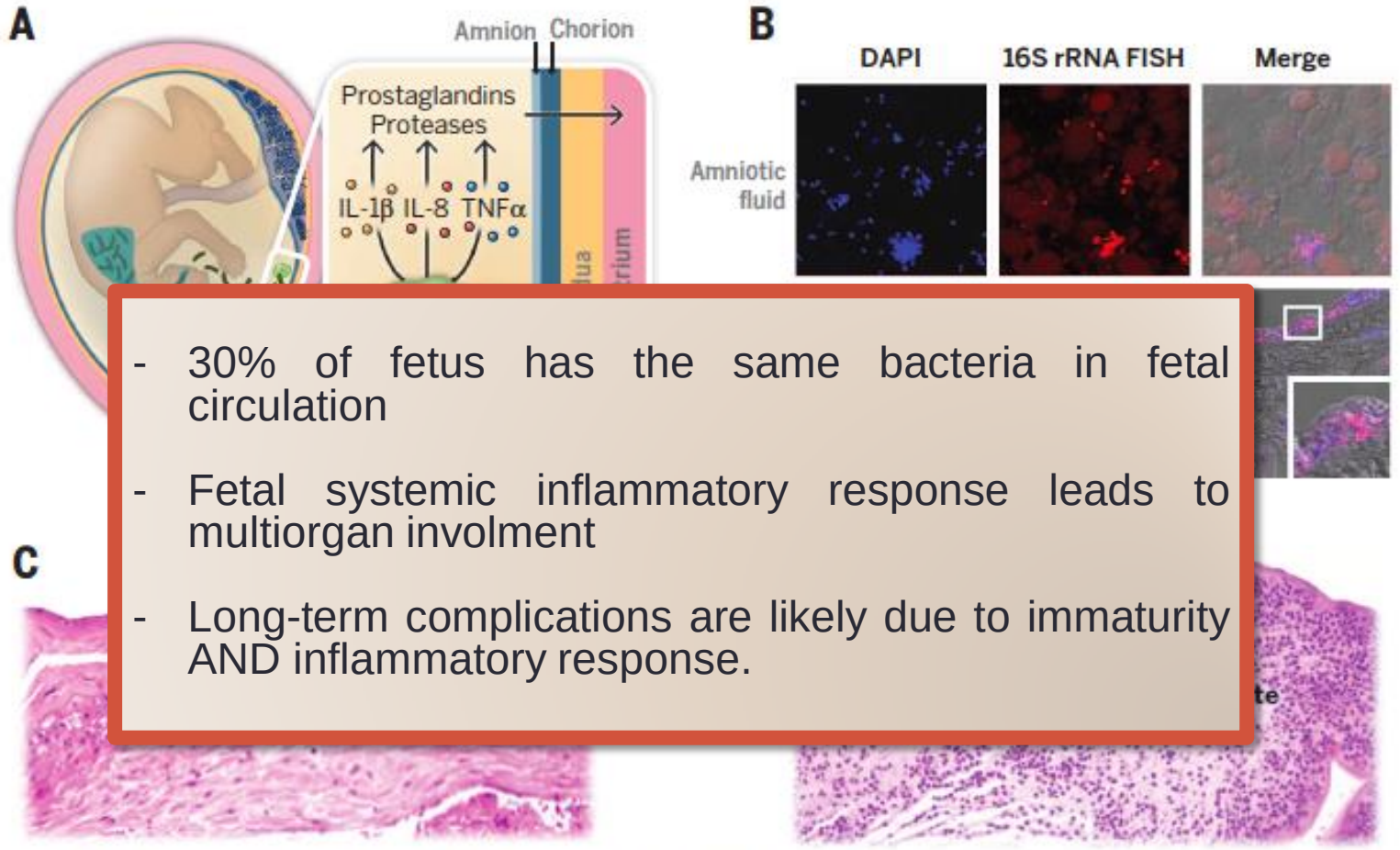


Fig. 3. Mechanisms of microbial-induced preterm labor. (**A**) Bacteria from the lower genital tract gain access to the amniotic cavity and stimulate the production of chemokines (IL-8 and CCL2) and cytokines (IL-1α and TNF-α), as well as other inflammatory mediators (prostaglandins and reactive oxygen radicals) and proteases. These products can initiate myometrial contractility and induce membrane rupture. (**B**) (Top left) Amniotic fluid containing bacteria that was retrieved by amniocentesis from a patient with preterm labor. Bacteria and nuclei stained with DAPI (4′,6-diamidino-2-phenylindole) (blue). (Top middle) Bacteria identified with a probe against 16*S* ribosomal RNA (rRNA) using fluorescent in situ hybridization. (Bottom left and middle) Bacteria invading the amnion epithelium. Note the absence of bacteria in the subepithelial part of the amnion, suggesting that the pathway of microbial invasion is ascending into the amniotic cavity (*74*). (**C**) Chorioamniotic membranes without evidence of inflammation. Amnion and chorion are identified. (**D**) A similar membrane section as (C) from a patient with intra-amniotic infection. Inflammatory cells from the mother infiltrate the chorion and amnion.

Microbial-induced inflammation



- 30% of fetus has the same bacteria in fetal circulation
- Fetal systemic inflammatory response leads to multiorgan involment
- Long-term complications are likely due to immaturity AND inflammatory response.

Fig. 3. Mechanisms of microbial-induced preterm labor. (**A**) Bacteria from the lower genital tract gain access to the amniotic cavity and stimulate the production of chemokines (IL-8 and CCL2) and cytokines (IL-1α and TNF-α), as well as other inflammatory mediators (prostaglandins and reactive oxygen radicals) and proteases. These products can initiate myometrial contractility and induce membrane rupture. (**B**) (Top left) Amniotic fluid containing bacteria that was retrieved by amniocentesis from a patient with preterm labor. Bacteria and nuclei stained with DAPI (4′,6-diamidino-2-phenylindole) (blue). (Top middle) Bacteria identified with a probe against 16*S* ribosomal RNA (rRNA) using fluorescent in situ hybridization. (Bottom left and middle) Bacteria invading the amnion epithelium. Note the absence of bacteria in the subepithelial part of the amnion, suggesting that the pathway of microbial invasion is ascending into the amniotic cavity (*74*). (**C**) Chorioamniotic membranes without evidence of inflammation. Amnion and chorion are identified. (**D**) A similar membrane section as (C) from a patient with intra-amniotic infection. Inflammatory cells from the mother infiltrate the chorion and amnion.

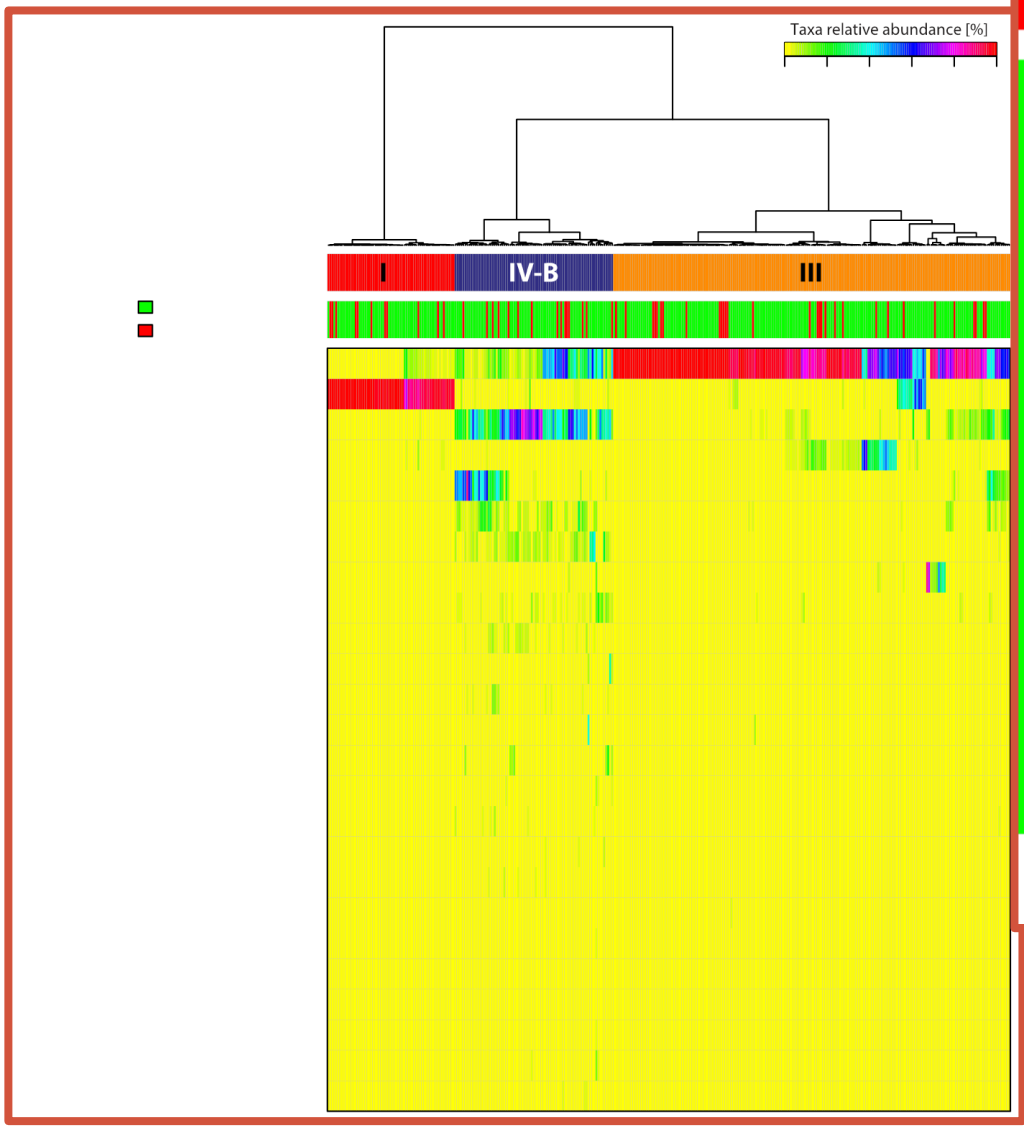
Why some women develop infection?

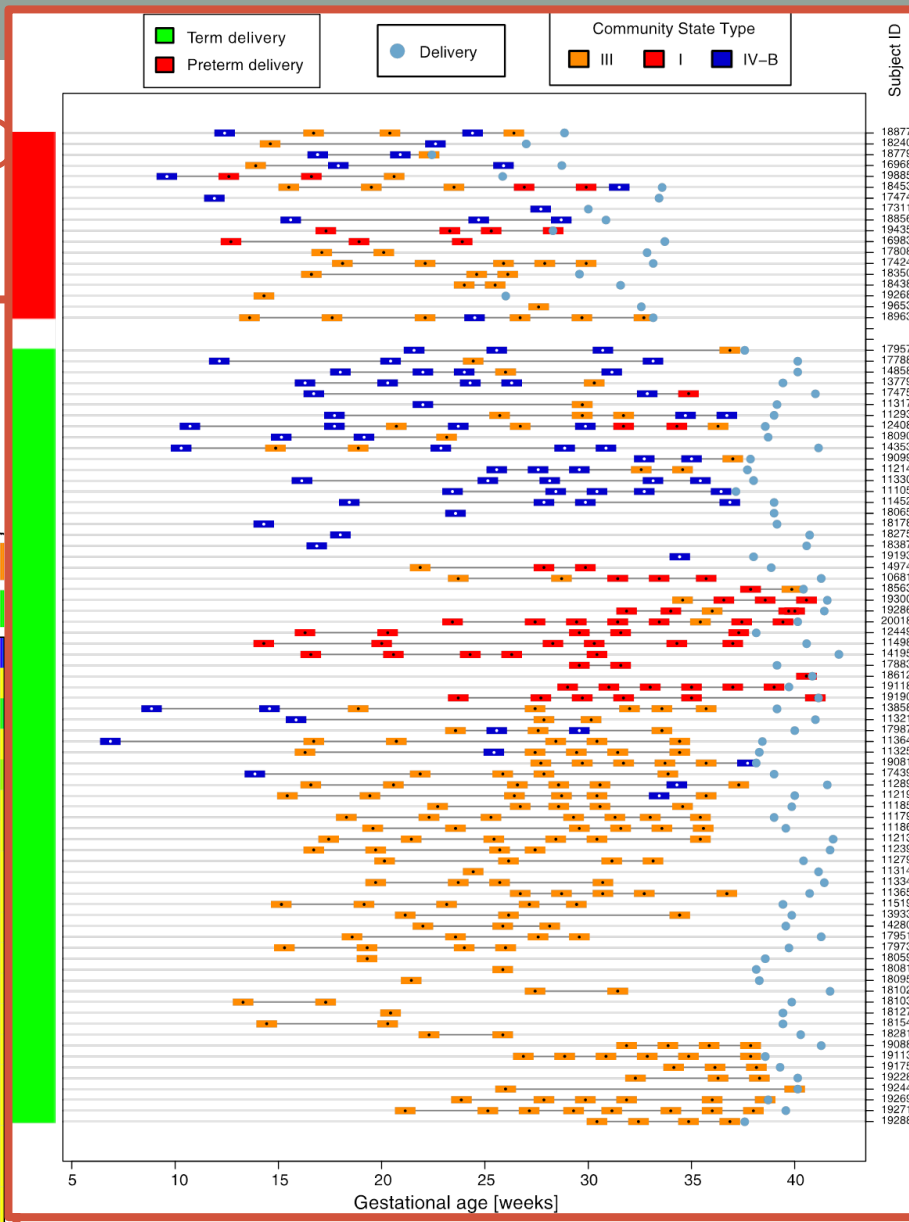
Key role of microbial ecosystem of the lower genital tract

- Before puberty: anaerobic bacteria prevalence
- After puberty: lactobacilli spp prevalence
- Vaginal microbiota of pregnant women is different from that of non-pregnant women
- The stability of the vaginal microbiota of pregnant women is higher than that of non-pregnant women
- Vaginal microbiota usually changes during pregnancy from one CST to antoher CST dominated by Lactobacillus spp

Preterm labour: one syndrome, many causes. Romero et al. – Science 2014. Aug 15;345(6198):760-5.
The composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women – Romero et al. Microbiome 2014

Why some women d





45(6198):760-5.

fferent from that of non-pregnant women – Romero et al. Microbiome

erm labor and delivery and those with a normal delivery at term – Romero

Romero et al. Microbiome 2014, 2:18
http://www.microbiomejournal.com/content/2/1/18

Microbiome

RESEARCH Open Access

The vaginal microbiota of pregnant women who subsequently have spontaneous preterm labor and delivery and those with a normal delivery at term

Abstract

Background: This study was undertaken to determine whether the vaginal microbiota of pregnant women who subsequently had a spontaneous preterm delivery is different from that of women who had a term delivery.

Results: This was a nested case–control study of pregnant women who had a term delivery (controls) and those who had a spontaneous preterm delivery before 34 weeks of gestation (cases). Samples of vaginal fluid were collected longitudinally and stored at −70°C until assayed. A microbial survey using pyrosequencing of V1-V3 regions of 16S rRNA genes was performed. We tested the hypothesis of whether the relative abundance of individual microbial species (phylotypes) was different between women who had a term versus preterm delivery. A suite of bioinformatic and statistical tools, including linear mixed effects models and generalized estimating equations, was used. We show that: 1) the composition of the vaginal microbiota during normal pregnancy changed as a function of gestational age, with an increase in the relative abundance of four *Lactobacillus* spp., and decreased in anaerobe or strict-anaerobe microbial species as pregnancy progressed; 2) no bacterial taxa differed in relative abundance between women who had a spontaneous preterm delivery and those who delivered at term; and 3) no differences in the frequency of the vaginal community state types (CST I, III, IV-B) between women who delivered at term and those who delivered preterm were detected.

Conclusions: The bacterial taxa composition and abundance of vaginal microbial communities, characterized with 16S rRNA gene sequence-based techniques, were not different in pregnant women who subsequently delivered a preterm neonate versus those who delivered at term.

Keywords: Infection-induced preterm delivery, Histologic chorioamnionitis, Prematurity, Vaginal flora, Vaginal microbiome

SCIENTIFIC REPORTS

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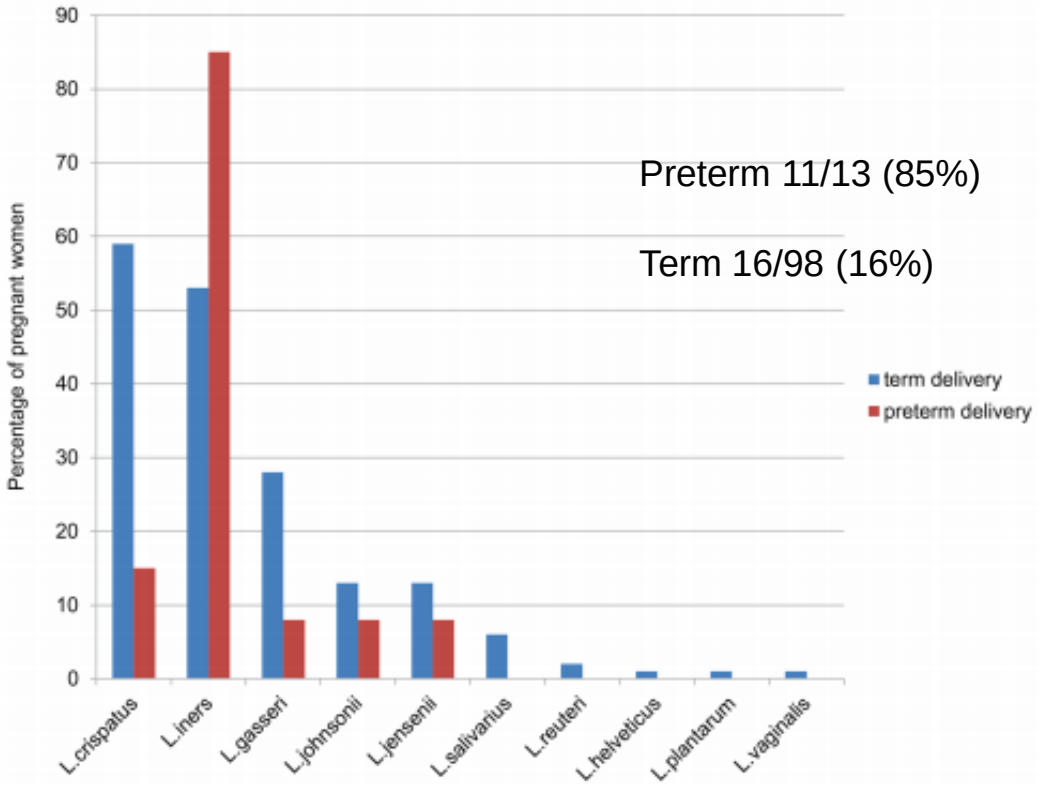
SUBJECT AREAS:
OUTCOMES RESEARCH
MEDICAL RESEARCH

Received
17 February 2014

Characterisation of the vaginal *Lactobacillus* microbiota associated with preterm delivery

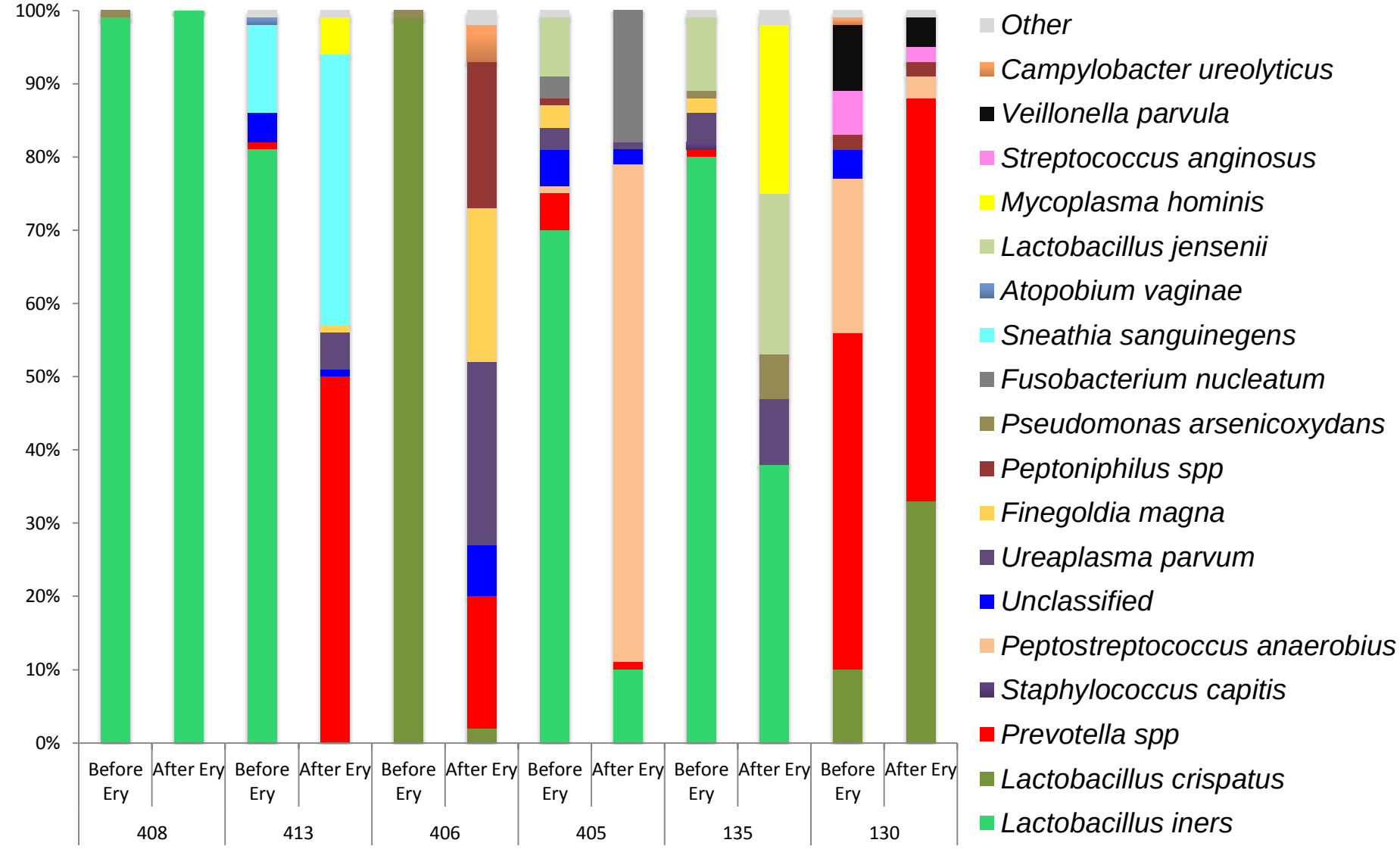
Ljubomir Petricevic[1], Konrad J. Domig[2], Franz Josef Nierscher[1], Michael J. Sandhofer[1], Maria Fidesser[2], Iris Krondorfer[2], Peter Husslein[1], Wolfgang Kneifel[2] & Herbert Kiss[1]



Preterm 11/13 (85%)

Term 16/98 (16%)

Stacked Bar Chart depicting percentage abundance of bacterial species in the vagina of patients with PPROM before and after Erythromycin



TNF-α polymorphism and bacterial vaginosis

AMERICAN JOURNAL of OBSTETRICS and GYNECOLOGY
www.elsevier.com/locate/ajog

A polymorphism in the promoter region of TNF and bacterial vaginosis: Preliminary evidence of gene-environment interaction in the etiology of spontaneous preterm birth

George A. Macones, MD, MSCE,* Samuel Parry, MD, Mohammed Elkousy, MD, Bonnie Clothier, MSN, CRNP, Serdar H. Ural, MD, Jerome F. Strauss III, MD, PhD

A case-control study on TNF-α polymorphism:

- Maternal carriers of the rarer allele (TNF-2) were at significantly increased risk of spontaneous preterm birth (OR 2.7, CI 95% 1.7-4.5)
- Women with **this genotype AND bacterial vaginosis** had increased risk of preterm birth compared with those who did not (OR 6.1, CI 95% 1.9-21.0)

What can we do? (1)

THE COCHRANE COLLABORATION®

Bacterial vaginosis confers risk for intra-amniotic infection and spontaneous preterm delivery

Cochrane Reviews → only one RCT available

(kiss 2004, 4155 women)

Antenatal lower genital tract infection screening and treatment program significantly reduces:

- preterm births (RR 0.55, 95%CI 0.41-0.75);
- Low birthweight infants (RR 0.48, 95%CI 0.34-0.66);
- very low birthweight infants (RR 0.34, 95%CI 0.15-0.75).

Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. *Cochrane Database of Systematic Reviews*, 2015

What can we do? (1)

THE COCHRANE COLLABORATION®

Bacterial vaginosis confers risk for intra-amniotic infection and spontaneous preterm delivery

Cochrane Reviews → only one RCT available

(kiss 2004, 4155 women)

AUTHORS' CONCLUSIONS

We are not able to determine the effects of recurrent or persistent infection on preterm birth

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- Low birthweight infants (RR 0.48, 95%CI 0.34-0.66);
- very low birthweight infants (RR 0.34, 95%CI 0.15-0.75).

Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. *Cochrane Database of Systematic Reviews*, 2015

Vaginal swab and preterm birth

International Journal of
GYNECOLOGY
& OBSTETRICS

www.elsevier.com/locate/ijgo

High vaginal swab cultures in normal and preterm labor

A.M. Bahar[a,*], N. Bilal[b], M.A. Eskander[a]

Table 1 Microorganisms isolated from women in preterm and term labor

Organism	Preterm labor (n=132), No. (%)	Term labor (n=136), no. (%)
No microorganism isolated	11 (8.3)	17 (12.5)
Group B streptococcus	6 (4.5)	6 (4.4)
Group A streptococcus	0 (0.0)	2 (1.5)
Enterococci	10 (7.6)	8 (5.9)
Staphylococcus aureus	28 (21.2)	34 (25)
Staphylococcus saprophyticus	8 (6.1)	10 (7.4)
Coagulase-negative staphylococcus	8 (6.1)	2 (1.5)
Escherichia coli	23 (17.4)	22 (16.2)
Klebsiella pneumoniae	14 (10.6)	10 (7.4)
Proteus	0 (0.0)	2 (1.5)
Serratia marcescens	14 (10.6)	8 (5.9)
Enterobacteria	11 (8.3)	4 (2.9)
Pseudomonas aeruginosa	2 (1.5)	4 (2.9)
Anaerobic Gram-positive cocci	6 (4.5)	5 (3.6)
Anaerobic Gram-negative rods	8 (6.0)	6 (4.4)
Mycoplasma hominis	23 (17.4)	31 (22.7)
Ureaplasma urealyticum	24 (18.2)	30 (22.1)
Chlamydia trachomatis	4 (3.0)	4 (2.9)

χ^2 tests=no difference.

Vaginal swab and preterm birth

International Journal of
GYNECOLOGY
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AUTHORS' CONCLUSIONS

No specific vaginal microorganism from those isolated was found to be **associated with preterm birth**; lower genital tract cultures provide poor prediction of fetal colonization.

Clinicians should not rely heavily on the result of high vaginal swab cultures when prescribing antibiotics to prevent fetal infection.

Table 1 Microorganisms isolated from women in preterm and term labor

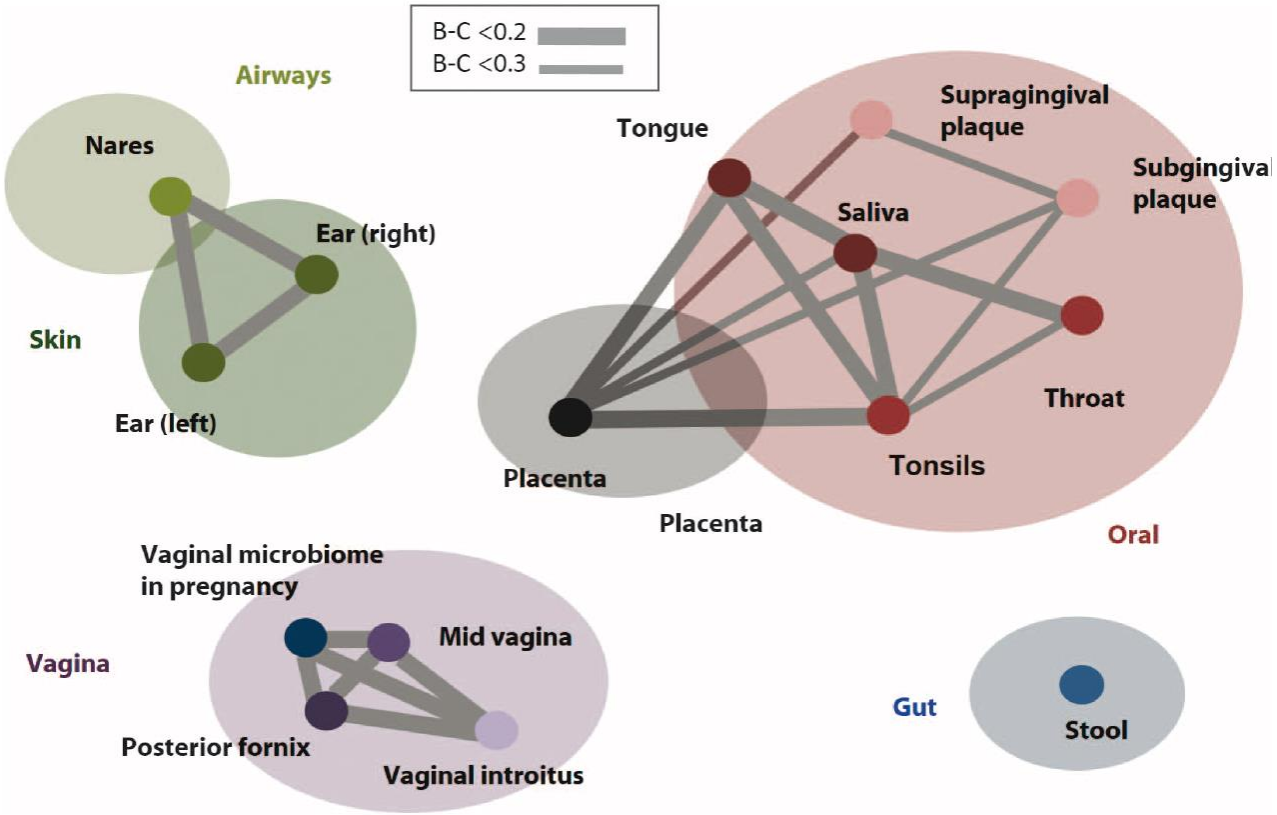
Organism	Preterm labor (*n*=132), No. (%)	Term labor (*n*=136), no. (%)
Pseudomonas aeruginosa	2 (1.5)	4 (2.9)
Anaerobic Gram-positive cocci	6 (4.5)	5 (3.6)
Anaerobic Gram-negative rods	8 (6.0)	6 (4.4)
Mycoplasma hominis	23 (17.4)	31 (22.7)
Ureaplasma urealyticum	24 (18.2)	30 (22.1)
Chlamydia trachomatis	4 (3.0)	4 (2.9)

χ^2 tests=no difference.

Are we going in the right direction?

The Placenta Harbors a Unique Microbiome

Kjersti Aagaard,[1,2,3]* Jun Ma,[1,2] Kathleen M. Antony,[1] Radhika Ganu,[1] Joseph Petrosino,[4] James Versalovic[5]



Sci Transl Med **6**, 237ra65 (2014)

What can we do? (2)

Bacterial vaginosis confers risk for intra-amniotic infection and spontaneous preterm delivery

Antibiotics for treating bacterial vaginosis in pregnancy (Cochrane)

21 trials were included (7847 women) showing that antibiotic therapy:

- eradicated bacterial vaginosis during pregnancy;
- **Did not** reduce the risk of preterm birth (PTB)
- **Did not** reduce the risk of preterm prelabour rupture of membranes
- In women with previous PTB **did not** affect the risk of subsequent PBT
- In women with abnormal vaginal flora treatment **MAY** reduce the risk of PTB
- Oral vs vaginal antibiotics **did not** reduce the risk of PTB
- Different frequency of dosing antibiotics showed no difference

Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database of Systematic Reviews*, 2013

THE COCHRANE COLLABORATION®

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Analysis 1.6. Comparison 1 Any antibiotic versus placebo/no treatment, Outcome 6 Preterm birth < 34 weeks.

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 1 Any antibiotic versus placebo/no treatment

Outcome: 6 Preterm birth < 34 weeks

Study or subgroup	Any antibiotic n/N	Placebo/no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Clindamycin (vaginal) versus placebo					
Vermeulen 1999	1/11	1/11		10.5 %	1.00 [0.07, 14.05]
Subtotal (95% CI)	**11**	**11**		**10.5 %**	**1.00 [0.07, 14.05]**
Total events: 1 (Any antibiotic), 1 (Placebo/no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Metronidazole (oral) versus placebo					
McDonald 1997	7/242	6/238		63.6 %	1.15 [0.39, 3.36]
Shennan 2006	4/8	2/5		25.9 %	1.25 [0.35, 4.49]
Subtotal (95% CI)	**250**	**243**		**89.5 %**	**1.18 [0.51, 2.74]**
Total events: 11 (Any antibiotic), 8 (Placebo/no treatment)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.38 (P = 0.71)					
Total (95% CI)	**261**	**254**		**100.0 %**	**1.16 [0.52, 2.59]**
Total events: 12 (Any antibiotic), 9 (Placebo/no treatment)					
Heterogeneity: Chi^2 = 0.03, df = 2 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 0.36 (P = 0.72)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.91), I^2 =0.0%					

- Oral vs vaginal antibiotics **did not** reduce the risk of PTB
- Different frequency of dosing antibiotics showed no difference

Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database of Systematic Reviews*, 2013

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Analysis 1.6. Comparison 1 Any antibiotic versus placebo/no treatment, Outcome 6 Preterm birth < 34

Review: Antibiotics for

Comparison: 1 Any ant

Outcome: 6 Preterm b

Study or subgroup

1 Clindamycin (vaginal) ve

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Subtotal (95% CI)

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Heterogeneity: not applic

Test for overall effect: Z =

2 Metronidazole (oral) ve

McDonald 1997

Shennan 2006

Subtotal (95% CI)

Total events: 11 (Any anti

Heterogeneity: Chi² = 0.0

Test for overall effect: Z =

Total (95% CI)

Total events: 12 (Any anti

Heterogeneity: Chi² = 0.0

Test for overall effect: Z =

Test for subgroup differen

Analysis 1.7. Comparison 1 Any antibiotic versus placebo/no treatment, Outcome 7 Preterm birth < 32 weeks.

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 1 Any antibiotic versus placebo/no treatment

Outcome: 7 Preterm birth < 32 weeks

Study or subgroup	Any antibiotic n/N	Placebo/no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Clindamycin (oral) versus placebo					
Ugwumadu 2003	9/244	6/241		13.2 %	1.48 [0.54, 4.10]
Subtotal (95% CI)	**244**	**241**		**13.2 %**	**1.48 [0.54, 4.10]**
Total events: 9 (Any antibiotic), 6 (Placebo/no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
2 Clindamycin (vaginal) versus placebo					
Joesoef 1995	16/340	9/341		19.6 %	1.78 [0.80, 3.98]
Subtotal (95% CI)	**340**	**341**		**19.6 %**	**1.78 [0.80, 3.98]**
Total events: 16 (Any antibiotic), 9 (Placebo/no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					
3 Metronidazole (oral) versus placebo					
McDonald 1997	5/242	5/238		11.0 %	0.98 [0.29, 3.35]
NICHD MFMU 2000	22/953	26/966		56.3 %	0.86 [0.49, 1.50]
Subtotal (95% CI)	**1195**	**1204**		**67.3 %**	**0.88 [0.53, 1.46]**
Total events: 27 (Any antibiotic), 31 (Placebo/no treatment)					
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0.0%					
Test for overall effect: Z = 0.50 (P = 0.62)					
Total (95% CI)	**1779**	**1786**		**100.0 %**	**1.13 [0.77, 1.68]**
Total events: 52 (Any antibiotic), 46 (Placebo/no treatment)					
Heterogeneity: Chi² = 2.49, df = 3 (P = 0.48); I² = 0.0%					
Test for overall effect: Z = 0.63 (P = 0.53)					
Test for subgroup differences: Chi² = 2.45, df = 2 (P = 0.29), I² = 18%					

0.1 0.2 0.5 1 2 5 10

Any antibiotic | Placebo/no treatment

- Oral vs
- Different

Antibiotics for treating bacter

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What we need? (2)

Analysis 2.2. Comparison 2 Antibiotic versus another antibiotic, Outcome 2 Preterm birth < 37 weeks.

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 2 Antibiotic versus another antibiotic

Outcome: 2 Preterm birth < 37 weeks

Study or subgroup	Metronidazole n/N	Clindamycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oral metronidazole versus oral clindamycin					
Darwish 2007	17/39	19/39		51.4 %	0.89 [0.55, 1.45]
Subtotal (95% CI)	**39**	**39**		**51.4 %**	**0.89 [0.55, 1.45]**
Total events: 17 (Metronidazole), 19 (Clindamycin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.45 (P = 0.65)					
2 Vaginal metronidazole versus vaginal clindamycin					
Darwish 2007	16/39	18/39		48.6 %	0.89 [0.54, 1.48]
Subtotal (95% CI)	**39**	**39**		**48.6 %**	**0.89 [0.54, 1.48]**
Total events: 16 (Metronidazole), 18 (Clindamycin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.65)					
Total (95% CI)	**78**	**78**		**100.0 %**	**0.89 [0.63, 1.26]**
Total events: 33 (Metronidazole), 37 (Clindamycin)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.99), I^2 =0.0%					

Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database of Systematic Reviews*, 2013

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Analysis 2.1. Comparison 2 Antibiotic versus another antibiotic, Outcome 1 Incidence of premature rupture of membranes.

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 2 Antibiotic versus another antibiotic

Outcome: 1 Incidence of premature rupture of membranes

Study or subgroup	Metronidazole n/N	Clindamycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oral metronidazole versus oral clindamycin					
Darwish 2007	22/39	20/39		48.8 %	1.10 [0.73, 1.66]
Subtotal (95% CI)	**39**	**39**		**48.8 %**	**1.10 [0.73, 1.66]**
Total events: 22 (Metronidazole), 20 (Clindamycin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.45 (P = 0.65)					
2 Vaginal metronidazole versus vaginal clindamycin					
Darwish 2007	23/39	21/39		51.2 %	1.10 [0.74, 1.62]
Subtotal (95% CI)	**39**	**39**		**51.2 %**	**1.10 [0.74, 1.62]**
Total events: 23 (Metronidazole), 21 (Clindamycin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.65)					
Total (95% CI)	**78**	**78**		**100.0 %**	**1.10 [0.83, 1.46]**
Total events: 45 (Metronidazole), 41 (Clindamycin)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.99), I^2 =0.0%					

Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database of Systematic Reviews*, 2013

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What can we do? (2)

Bacterial vaginosis confers risk for intra-amniotic infection and spontaneous preterm delivery

Antibiotics for treating bacterial vaginosis in pregnancy (Cochrane)

21 trials were included (7847 women) showing that

AUTHORS' CONCLUSIONS

Antibiotic treatment can eradicate bacterial vaginosis in pregnancy.

The overall risk of PTB was not significantly reduced.

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t PBT

- In women with abnormal vaginal flora treatment MAY reduce the risk of PTB
- Oral vs vaginal antibiotics **did not** reduce the risk of PTB
- Different frequency of dosing antibiotics showed no difference

Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database of Systematic Reviews*, 2013

THE COCHRANE COLLABORATION®

What can we do? (3)

Antibiotic prophylaxis during the second and the thrid trimester to reduce adverse pregnancy outcomes and morbidity (2015)

Antibiotic prophylaxis administered between 14 to 34 weeks of pregnancy (Cochrane)

Seven trials were included (app. 2100 women) showing that antibiotic prophylaxis:

- **Did not** reduce the risk of preterm birth (PTB)
- **Did not** reduce the risk of preterm prelabour rupture of membranes
- **Reduced** preterm delivery in women with previous PTB **and** a bacterial vaginosis during the current pregnancy
- **Did not** reduce the risk of preterm delivery in women with previous PTB without a bacterial imbalance during the current pregnancy
- Reduced postpartum endometritis
- **Did not** reduce neonatal illness.

Antibiotic prophylaxis during the second and the thrid trimester to reduce adverse pregnancy outcomes and morbidity. *Cochrane Database of Systematic Reviiws*, 2015

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previous PTB **and** a

women with previous
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Analysis 1.2. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 2 Preterm delivery.

Review: Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 2 Preterm delivery

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Unselected pregnant women					
McGregor 1990	8/119	9/110		7.8 %	0.82 [0.33, 2.05]
Paul 1997	21/159	17/164		14.3 %	1.27 [0.70, 2.32]
Sen 2005	6/89	8/81		6.6 %	0.68 [0.25, 1.88]
Subtotal (95% CI)	**367**	**355**		**28.7 %**	**1.01 [0.65, 1.59]**
Total events: 35 (Treatment), 34 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 1.34, df = 2 (P = 0.51); I² =0.0%					
Test for overall effect: Z = 0.06 (P = 0.95)					
2 High-risk pregnant women with BV and weight before pregnancy less than 50 kg					
Hauth 1995	7/51	10/30		8.7 %	0.41 [0.18, 0.97]
Subtotal (95% CI)	**51**	**30**		**8.7 %**	**0.41 [0.18, 0.97]**
Total events: 7 (Treatment), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.04 (P = 0.042)					
3 High-risk pregnant women with BV and weight before pregnancy more than 50 kg					
Hauth 1995	47/121	32/56		26.3 %	0.68 [0.49, 0.93]
Subtotal (95% CI)	**121**	**56**		**26.3 %**	**0.68 [0.49, 0.93]**
Total events: 47 (Treatment), 32 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.38 (P = 0.018)					
4 High-risk pregnant women with previous preterm delivery					
Hauth 1995	56/254	26/104		21.9 %	0.88 [0.59, 1.32]
Vermeulen 1999	20/70	14/72		14.4 %	1.47 [0.81, 2.67]
Subtotal (95% CI)	**324**	**176**		**36.3 %**	**1.08 [0.66, 1.77]**
Total events: 76 (Treatment), 40 (Control)					
Heterogeneity: Tau² = 0.06; Chi² = 1.92, df = 1 (P = 0.17); I² =48%					
Test for overall effect: Z = 0.32 (P = 0.75)					
Total (95% CI)	**863**	**617**		**100.0 %**	**0.85 [0.64, 1.14]**
Total events: 165 (Treatment), 116 (Control)					
Heterogeneity: Tau² = 0.05; Chi² = 9.94, df = 6 (P = 0.13); I² =40%					
Test for overall effect: Z = 1.07 (P = 0.28)					
Test for subgroup differences: Chi² = 5.85, df = 3 (P = 0.12), I² =49%					

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Favours treatment Favours control

Antib orbidity. *Cochrane Database of Systematic Reviiws*, 2015

Analysis 1.2. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 2 Preterm delivery.

Review: Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity

Comparison:

Outcome:

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Favours treatment Favours control

Analysis 1.1. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 1 Preterm prelabour rupture of membranes.

Review: Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 1 Preterm prelabour rupture of membranes

Study or subgroup	Favours treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Unselected pregnant women					
McGregor 1990	2/119	6/110		100.0 %	0.31 [0.06, 1.49]
Subtotal (95% CI)	**119**	**110**		**100.0 %**	**0.31 [0.06, 1.49]**
Total events: 2 (Favours treatment), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.46 (P = 0.14)					
2 High-risk pregnant women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**119**	**110**		**100.0 %**	**0.31 [0.06, 1.49]**
Total events: 2 (Favours treatment), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.46 (P = 0.14)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Antib orbidity. *Cochrane Database of Systematic Reviiws*, 2015

What can we do? (3)

Antibiotic prophylaxis during the second and the thrid trimester to reduce adverse pregnancy outcomes and morbidity (2015)

Antibiotic prophylaxis administered between 14 to 34 weeks of pregnancy (Cochrane)

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AUTHORS' CONCLUSIONS

There is, therefore**, no justification to give antibiotics** to all pregnant women during the second or the third trimester to prevent adverse infectious effects on pregnancy outcomes.

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- **Did not** reduce the risk of preterm delivery in women with previous PTB without a bacterial imbalance during the current pregnancy
- Reduced postpartum endometritis
- **Did not** reduce neonatal illness.

Antibiotic prophylaxis during the second and the thrid trimester to reduce adverse pregnancy outcomes and morbidity. *Cochrane Database of Systematic Reviiws*, 2015

Lattobacilli and their protective role

- Protective mechanism of lattobacilli are:
  - Blocking pathogen attachement to the epithelium
  - Producing H2O2
  - Producing bacteriocins

- Hydrogen-peroxyde-producing Lattobacilli are associated with lower prevalence rate of
  - Bacterial vaginosis
  - Urinary tract infections

Probiotics and preterm labour

THE COCHRANE COLLABORATION®

Probiotics have been shown to displace and kill vaginal pathogen and modulate inflammatory host response

Probiotics for preventing preterm labour (Cochrane)

Three trials were included (344 women) showing:

- No statistically significant effects on preterm birth (<37 wks) and very preterm birth (<32 wks);
- Not estimable effects on neonatal death or severe moribidity
- Reduced risk of genital infection with probiotics (RR 0.19, CI 95% 0.08-0.48)
- Reduced risk of genital infection with vaginal yogurt (RR 0.20; 95% CI 0.08 to 0.52) compared with acetic acid
- Not statistically significant reduction in genital infection with oral yogurt

Probiotics for preventing preterm labour. *Cochrane Database of Systematic Reviiws*, 2010

Probiotics and preterm labour

Probiotics have been shown to displace and kill vaginal pathogen and modulate inflammatory host response

Probiotics for preventing preterm labour (Cochrane)

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- No statistically significant effects on preterm birth (<37 wks) and very p
- N
- R 5% 0
- R CI 0.08 to 0.52) compared with acetic acid
- Not statistically significant reduction in genital infection with oral yogurt

AUTHORS' CONCLUSIONS

Although the use of probiotics appears to treat vaginal infections in pregnancy, **there are currently no data** from trials to assess any impact on preterm labour.

Probiotics for preventing preterm labour. *Cochrane Database of Systematic Reviiws*, 2010

Asymptomatic bacteriuria in pregnancy

- At least 100.000 CFU/mL of the same bacterial strain in 2 consecutively voided urine specimens
- 2-7% of pregnancies in the first trimester
- 5-10% of all pregnancies
- 20-30% progress to pyelonephritis if left untreated
- **Screening at 12 to 16 weeks' gestation is recommended**
- Usually isolated: enterobacters, other G- and G+ bacteria
- Untreated group B streptococcus bacteriuria is associated with chorioamnionitis, infection in the placenta or amniotic fluid

Treatment for asymptomatic bacteriuria

THE COCHRANE COLLABORATION®

20-30% progress to pyelonephritis if left untreated

- Antibiotic treatment is effective in clearing asymptomatic bacteriuria (RR 0.25, 95% CI 0.14-0.48)
- There is a reduction of the incidence of pyelonephritis (RR 0.23, 95% CI 0.49-0.89)
- Reduction in low birthweight babies (RR 0.66, CI 95% 0.49-0.89)
- No significant difference with different antibiotics
- Single-dose regimen MAY be less effective than seven-day regimen
- **No reduction in preterm birth**

Antibiotics for asymptomatic bacteriuria in pregnancy – Cochrane Databaes Syst Rev. 2007 Apr 18; (2): CD000490

Different antibioitc regimens for treating asymptomatic bacteriuria in pregnancy – Cochrane Databaes Syst Rev. 2010 Sept 8; (9): CD007855

Duration of treatment for asymptomatic bacteriuria during pregnancy – Cochrane Databaes Syst Rev. 2011 Dec 7; (12): CD000491

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