



**CAIRO  
IAMANEH-2006**

**INFECTION IN PREGNANCY:  
PREVENTION AND MANAGEMENT OF GBS**

**GC DI RENZO, ITALY**

**Several large epidemiological studies have documented that women with an altered vaginal ecosystem are at increased risk of pregnancy complications**

(preterm birth – amnionitis - post partum infections)



# Association between bacterial vaginosis and placental and amniotic fluid infection

Year	Outcome	OR (95% CI)
1988	Chorioamnionitis	2.6 (1.0 – 6.6)
1988	Chorioamnion infection	3.2 (1.1 – 6.6)
1990	Amnionitis	6.8 (3.6 – 12.7)

# Genital tract colonization of group B streptococci and preterm delivery

	<b>Preterm labor (%)</b>	<b>Preterm delivery (%)</b>	<b>PROM (%)</b>
<b>GBS pos.</b>	<b>6-21</b>	<b>5.4-6.5</b>	<b>5.6-16</b>
<b>GBS neg.</b>	<b>0-11</b>	<b>1.26-6.4</b>	<b>1.7-8.8</b>

**GBS, Group B streptococci**

Modified from Gibbs et al. Am J Obstet Gynecol 1992; 166: 1515-28



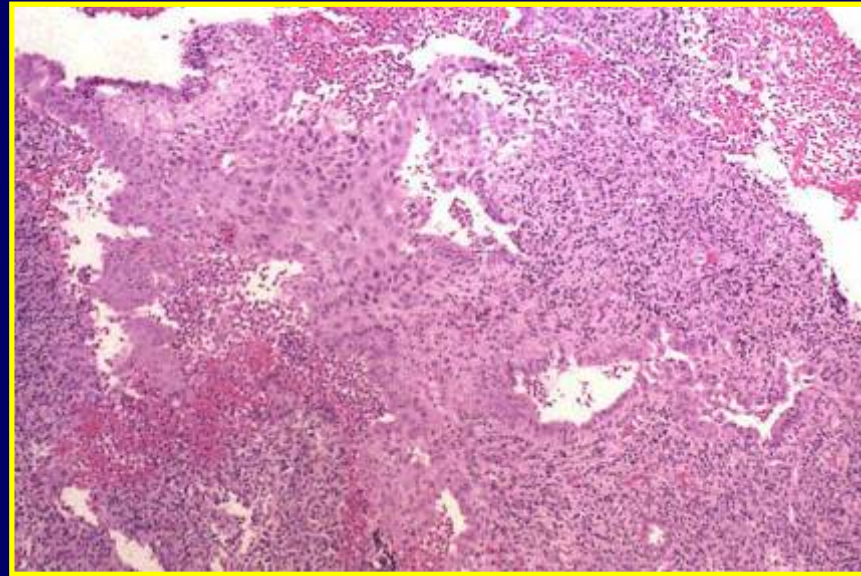
# BACTERIAL VAGINOSIS

- Prevotella
- Porphyromonas
- Peptostreptococcus
- Mobiluncus
- Mycoplasma hominis
- Gardnerella
- Bacteroides
- Veillonella

## Other associated pathogens:

- Trichomonas vaginalis
- Streptococcus
- Chlamydia trachomatis
- Neisseria gonorrhoeae
- Escherichia coli
- Candida albicans

# Infection as a Noxious Stimuli



- BV is 2 times more prevalent among African Americans
- Higher prevalence not explained by known behaviors or risk factors
- High BV rates in African American women may account for up to 30% excess risk of PTD

# VAGINOSIS:

## OBSTETRICAL AND GYNECOLOGICAL DISORDERS

### Obstetrical

- Chorioamnionitis
- Preterm labor
- Rupture of the membranes
- Postpartum endometritis
- Postpartum infections

### Gynecological

- Abnormal vaginal secretions
- Mucopurulent cervicitis
- Recurrent urinary tract infection
- Postoperative infections
- Post hysterectomy cellulitis of the vaginal vault
- Endometritis
- Pelvic Inflammatory Disease

**LOWER REPRODUCTIVE TRACT INFECTIONS  
(CERVICITIS-VAGINITIS)**

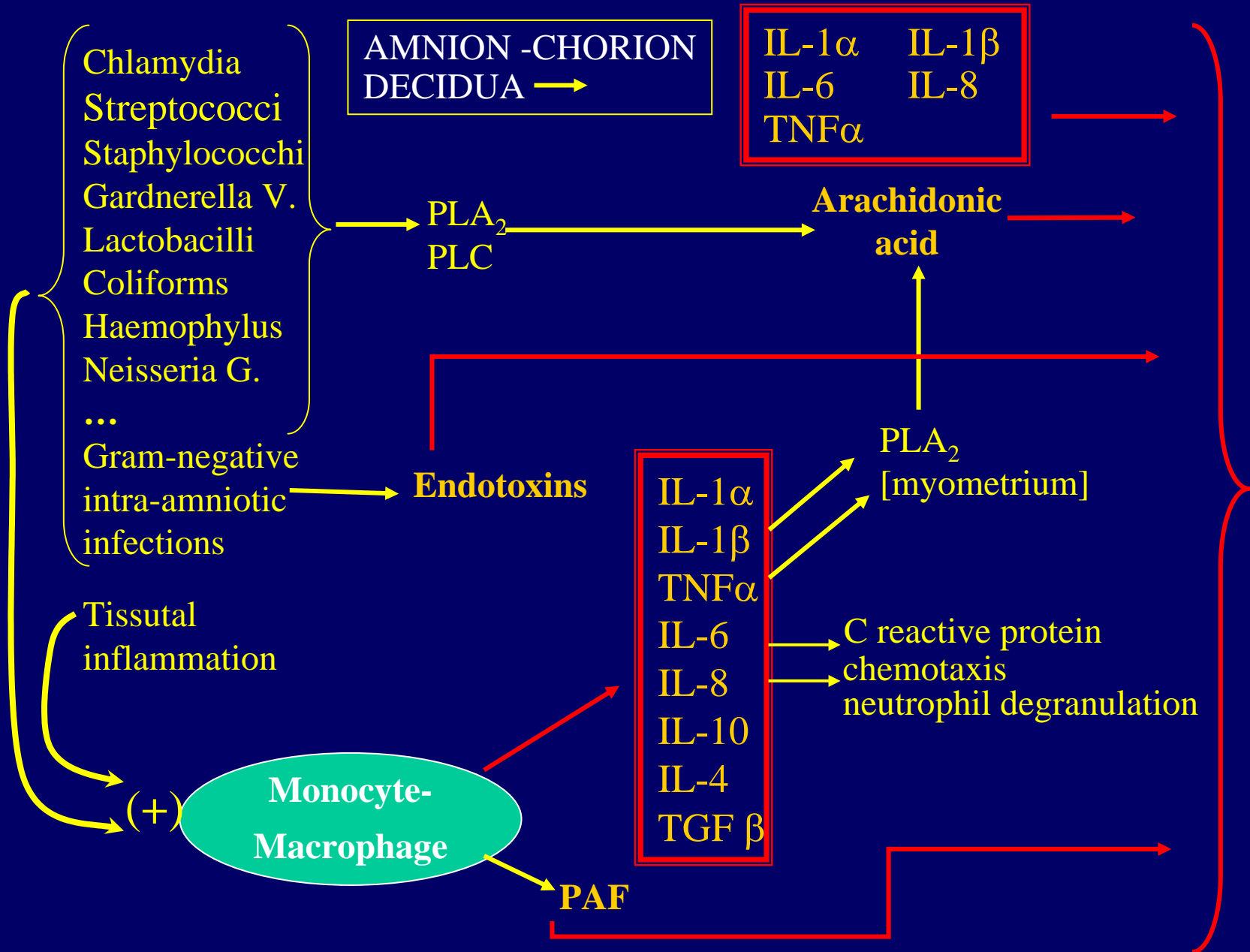


**INFLAMMATION OF UPPER GENITAL TRACT**



**PRETERM LABOR – PROM – PRETERM BIRTH**

# Citokines and preterm delivery



PGE<sub>2</sub> $\alpha$  - PGF<sub>2</sub> synthesis



**Amnion**

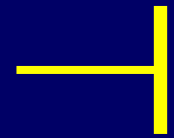
**Chorion**

**Decidua**

**Myometrium**

**Pregnancy  
at term**

$PG_s$



$PG$



**Contractility**

**Preterm  
no infection**

$PG_s$



$PG_s$



**Preterm  
infection**



# Microbiological assessment

## Separated vaginal and cervical swabs for recovery

- aerobic bacteria
- genital Mycoplasma
- Chlamydia trachomatis
- yeast
- Streptococci group B

**1830 pregnant women (8-14 and 30-34 wks)**

**30% of microbiological positivity**



**GARDNERELLA V.**

**MYCOPLASMA H.**

**UREAPLASMA U.**

**CHLAMYDIA T.**

**TRICHOMONAS V.**

**STREPTOCOCCUS B**



**52%**

**THREATENING PRETERM LABOR**

# New approaches to screen for preterm labor and PROM

- **Fetal fibronectin**
- **PROM test**
- **Bacterial enzymes**

# Bacterial enzymes

- **Mucinase**
  - **Sialidase**
  - **Protease**
  - **Collagenase**
- } **Mucolytic enzymes**

**Vaginal homeostasis**



**Lactobacilli**



**pH 3.7 – 4.2**

# Vaginal pH may be increased in response to several factors:

- **sexual intercourse**
- **antibiotic treatment**
- **inflammatory reactions**
- **microorganisms**

**Vaginal pH values were obtained by colorimetric reading of paper strips carried by special gloves**

**Cut-off point of pH  $\longrightarrow$  4,5**

**750 pregnant women** —————> **35% pH greater than 4,6**

**Only 28%**

**Signs and symptoms of vaginitis**

# Vaginal pH was positive (>4.6) in:

**Bacterial vaginosis** 75%

**Chlamydia trachomatis** 45%

**Streptococco group “B”** 53%

**Fungal vaginitis** 16%

**Escherichia coli** 60%



# GBS:

who, when and which  
approach should be used  
for GBS screening  
and intrapartum therapy?

**Group B *Streptococcus* (GBS) is usually a commensal bacterium that asymptotically colonizes the vaginal or rectal areas of 10-30% of pregnant women.**

**In these women, GBS can cause preterm labor, chorioamnionitis, postpartum endometritis, postpartum wound infection and sepsis.**

**At birth, approximately 50% of infants who are born to colonized mothers will also become colonized on their mucosal surface and the skin.**

**The vast majority of colonized newborns remain free of symptoms, whereas approximately 1% will develop invasive disease.**

**In addition to acute illness due to GBS, which is itself costly,  
GBS infections in newborns can result in  
death, disability and, in rare instance, recurrence of infections.  
Recent studies on death among newborns suggest fatality ratios  
ranging from 4 to 6% for cases identified  
by population-based surveillance during the 1990s.  
Surviving infants may have long-term development disabilities,  
such as mental retardation or hearing or vision loss.**

**The most important predictive circumstance  
that leads to neonatal GBS disease  
is the exposure of the newborn  
to the microorganism in the birth canal.**

**Ascending spread of GBS or increase of the inoculum  
to which the infant is exposed  
may be facilitated by some obstetric manipulations,  
such as intrauterine monitoring  
and numerous vaginal examinations.**

**Maternal bacteriuria due to GBS**  
**is likely indicative of a large inoculum**  
**present in the genital tract**  
**and is also associated**  
**with a higher risk for early-onset GBS disease.**

**RISK-BASED  
AND  
GBS CULTURE-BASED  
SCREENING METHODS**

# ACOG and AAP GUIDELINES

Prevention strategy using risk factors without prenatal culture screening

## One or more of the following:

- Previous infant with invasive GBS disease?
- GBS bacteriuria this pregnancy?
- Delivery < 37 weeks of gestation?
- Duration of ruptured membranes > 18 hours?
- Intrapartum temperature >38°C?

YES



**Give intrapartum  
prophylaxis**

NO



**NO intrapartum prophylaxis**

From CDC 2002

# RISK-BASED SCREENING

- Spontaneous onset of PTL RR: 10
- Prolonged rupture of membranes RR: 26
- Maternal fever RR: 10
- Previous affected baby RR: 5

# ACOG and AAP GUIDELINES

Prevention strategy using prenatal culture screening at 35 to 37 weeks of gestation

## Risk factors:

- Previous infant with invasive GBS disease?
- GBS bacteriuria this pregnancy?
- Delivery <37 weeks of gestation?

YES



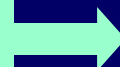
Give intrapartum penicillin

NO



Collect vaginal and rectal swab for GBS culture at 35-37 weeks of gestation

GBS +



Offer intrapartum penicillin

Not done, incomplete, or result unknown

## Risk factors:

- Intrapartum temperature >38°C?
- Membrane rupture > 18 hrs?

NO



Give intrapartum penicillin

GBS -



NO intrapartum prophylaxis needed

From CDC 2002

# NO SCREENING

- 8-10 cases per 10,000 livebirths
- 60 neonatal deaths annually in GB

# Risk factors for early onset GBS disease

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<b>Risk factor</b>	<b>%</b>
Maternal fever > 38°C	7,7
GBS on high vaginal swab	41
Prolonged rupture of membranes > 24 h	23,1
Pre-term labour	12,8
GBS urinary tract infection	2,5
GBS in previous pregnancy	10,2
None	2,5

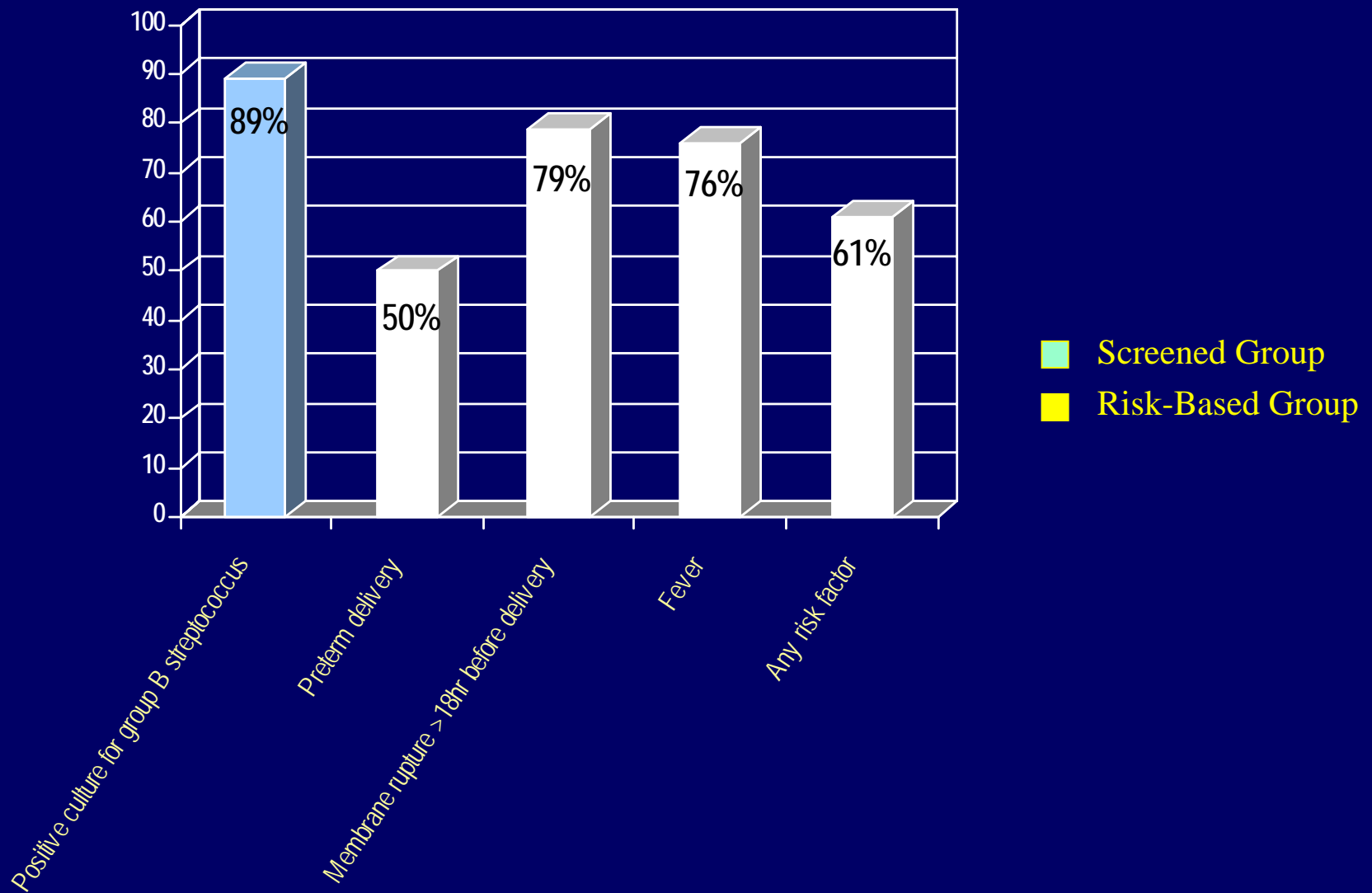
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## Neonatal outcomes related to infection before and after implementation of a combined GBS prevention protocol

Outcome	1994: Before GBS prophylaxis (n=13,887)		1995: After GBS prophylaxis (n=13,527)		<i>P</i> value
	No.	Rate X 1000	No.	Rate X 1000	
<b>Early-onset sepsis (<math>\leq 3</math> d)</b>					
GBS	31	2.2	6	0.4	.0001
Other organisms	29	2.1	14	1.0	.028
Total	60	4.3	20	1.5	.0001
<b>Late-onset GBS (4-30 d)</b>					
Meningitis	8	0.6	2	0.1	.063
Total	13	0.9	5	0.4	.067
<b>Neonatal deaths</b>					
GBS	3	0.2	0	0	.087
Sepsis, not GBS	3	0.2	5	0.4	.457
Total	36	2.6	30	2.2	.527

# Early-onset neonatal GBS infection in relation to prematurity, maternal race, and implementation of a combined GBS prophylaxis protocol

Factor	1994 Early-onset GBS neonatal infections		1995 Early-onset GBS neonatal infections		Significance		
	No.	Rate X 1000	No.	Rate X 1000	<i>P value</i>	<i>OR</i>	<i>95% CI</i>
<b>Cases</b>	13		0				
Preterm delivery	1,352	9.6	1,129	0	.0004	22.8	1.4 – 383.3
<b>Cases</b>	18		6				
Term delivery	12,535	1.4	12,398	0.5	.023	3.0	1.1 – 9.1
<b>Maternal race</b>							
Hispanic	15	1.7	3	0.3	.004	5.3	1.5 – 28.3
African American	12	3.4	3	1.0	.040	3.5	0.95 – 19.6
White	4	3.1	0	0	.14	6.7	0.4 – 125.0



**Proportion of Women in the Screened Group and the Risk-Based Group with Indications for Chemoprophylaxis Who Received Intrapartum Antibiotics.**

**Preterm delivery was defined as delivery at less than 37 weeks of gestation.**

**Fever was defined as an intrapartum temperature of 38°C or higher.**

**“Any risk factor” includes group B streptococcal bacteriuria during the current pregnancy and having previously had an infant with group B streptococcal disease.**

**Since the most accurate cultures  
are those collected within 5 weeks of delivery  
and since preterm delivery can be addressed empirically  
if negative culture results are not yet available,  
collection of prenatal cultures at 35 to 37 weeks' gestation  
is now recommended by CDC to improve  
the sensitivity and specificity  
of women who remained colonized at the time of delivery.**



## Identification

Species	Pigmented colonies (Instant Granada Medium)	$\beta$ -hemolytic colonies (Agar- blood)
GBS 1/82	yes	yes
COH31 r/s	yes	yes
COH31 r/s cl 12	no	no
<i>S. pyogenes</i>	no	yes
<i>S. aureus</i>	no	yes
<i>E. faecalis</i>	no	no
<i>E. coli</i>	no	no

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## Nr of colonies

Species	Dilution	Instant Granada Medium	Agar-blood
GBS 1/82	$1/10^7$	19	20
	$1/10^8$	3	4
	$1/10^9$	0	0

	Positive culture on blood-agar	Negative culture on blood-agar
Positive culture Granada Medium	24	2
Negative culture Granada Medium	0	34

**The use of a commercially available medium  
(Instant Granada Medium, Biomedics, Madrid, Spain)  
led to a rapid (~18h) and low-cost GBS identification  
from vaginal specimens,  
with 100% of both sensitivity and specificity.**

More recently, real-time polymerase chain reaction (PCR) techniques have become available.

It has been demonstrated that rapid PCR reliably identified group B streptococcal colonization in pregnant women with ruptured and unruptured membranes.

The FDA has approved the IDI-Strep B™ rapid PCR assay as equivalent to the Strep B OIA for rapid detection of GBS DNA in vaginal and rectal specimens from prepartum or intrapartum women.

The newly approved rapid PCR assay (IDI-Strep B™ PCR) has much greater sensitivity, particularly when used to evaluate rectovaginal samples, but this test also needs improvement before rapid PCR on vaginal specimens can be recommended as a replacement for antepartum cultures of rectovaginal specimens. Although promising, the role of rapid PCR in strategies for prevention of early-onset GBS infections remains to be delineated. In their current implementations, neither OIA nor PCR has sufficient sensitivity for intrapartum detection of vaginal GBS colonization.

# OIA and PCR test performance characteristics compared to enhancement broth cultures (95% CI)

	<b>OIA</b>	<b>PCR</b>
Sensitivity	0.071 (0.054 – 0.095)	0.625 (0.485 – 0.748)
Specificity	0.981 (0.976 – 0.984)	0.973 (0.943 – 0.988)
Positive predictive value	0.444 (0.315 – 0.580)	0.833 (0.680 – 0.925)
Negative predictive value	0.830 (0.782 – 0.869)	0.923 (0.883 – 0.951)
Bayesian likelihood ratios:		
Positive results	2.50	4.69
Negative results	0.956	0.433
McNemar's Test (P for difference from culture)*	< 0.001	0.014

\*OIA and PCR results also differed (McNemar's  $P < 0.001$ )

**ANTIBIOTIC  
SUSCEPTIBILITY**

# Recommended regimens for intrapartum antimicrobial prophylaxis for perinatal GBS disease prevention

Recommended

PENICILLIN G, 5 million units IV initial dose,  
then 2.5 million units IV every 4 hours until delivery

Alternative

AMPICILLIN, 2g IV initial dose,  
then 1g IV every 4 hours until delivery

## If penicillin allergic

- patients not at high risk for anaphylaxis

CEFAZOLIN, 2g IV initial dose,  
then 1g IV every 8 hours until delivery

- patients not at high risk for anaphylaxis

• GBS susceptible to clindamycin and erythromycin

CLINDAMYCIN, 900mg IV  
every 8 hours until delivery

**OR**

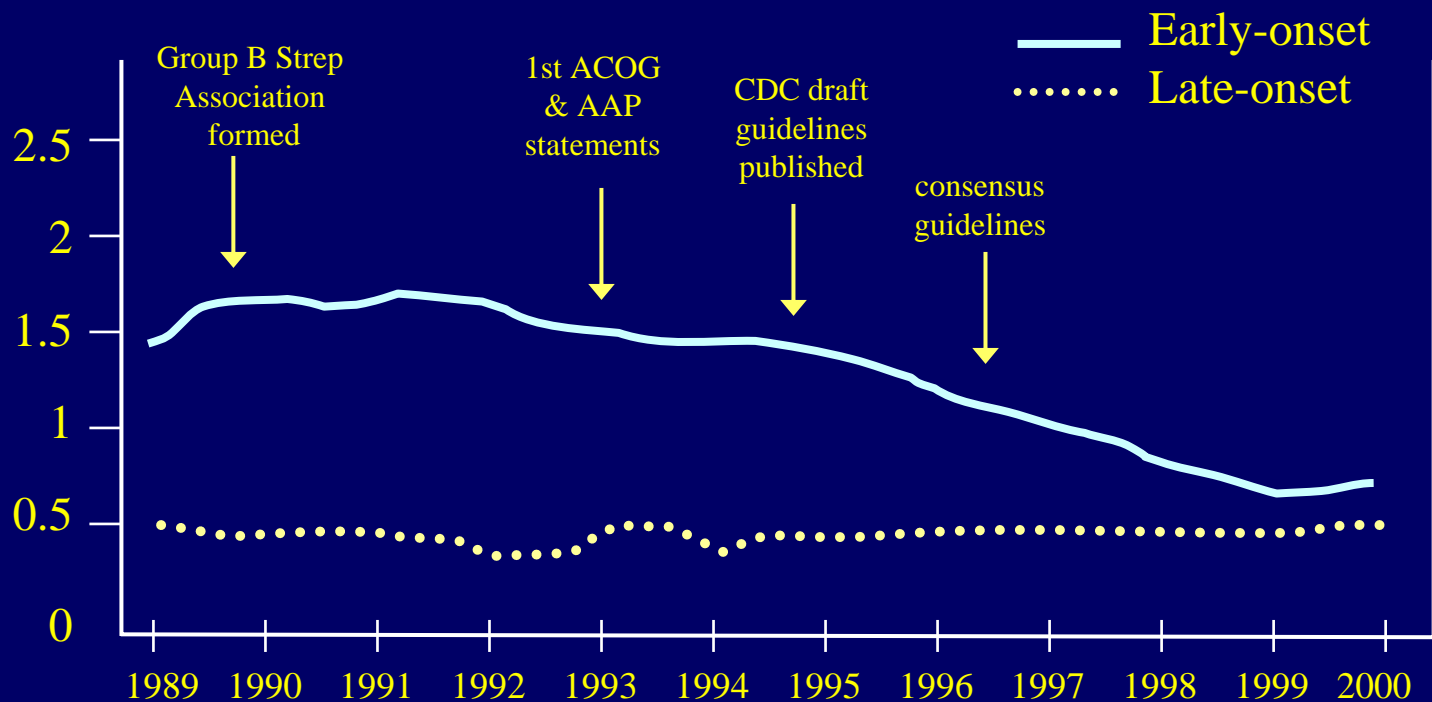
ERYTHROMYCIN, 500mg IV  
every 6 hours until delivery

• GBS resistant to clindamycin or erythromycin  
or susceptibility unknown

VANCOMYCIN, 1g IV  
every 12 hours until delivery

**ANTE-INTRAPARTUM  
CHEMOPROPHYLAXIS**

# Incidence of early- and late- onset invasive group B streptococcal disease-selected Active Bacterial Core surveillance areas, 1989-2000, and activities for prevention of group B streptococcal disease



# Trends in neonatal sepsis incidence in the era of perinatal GBS disease prevention

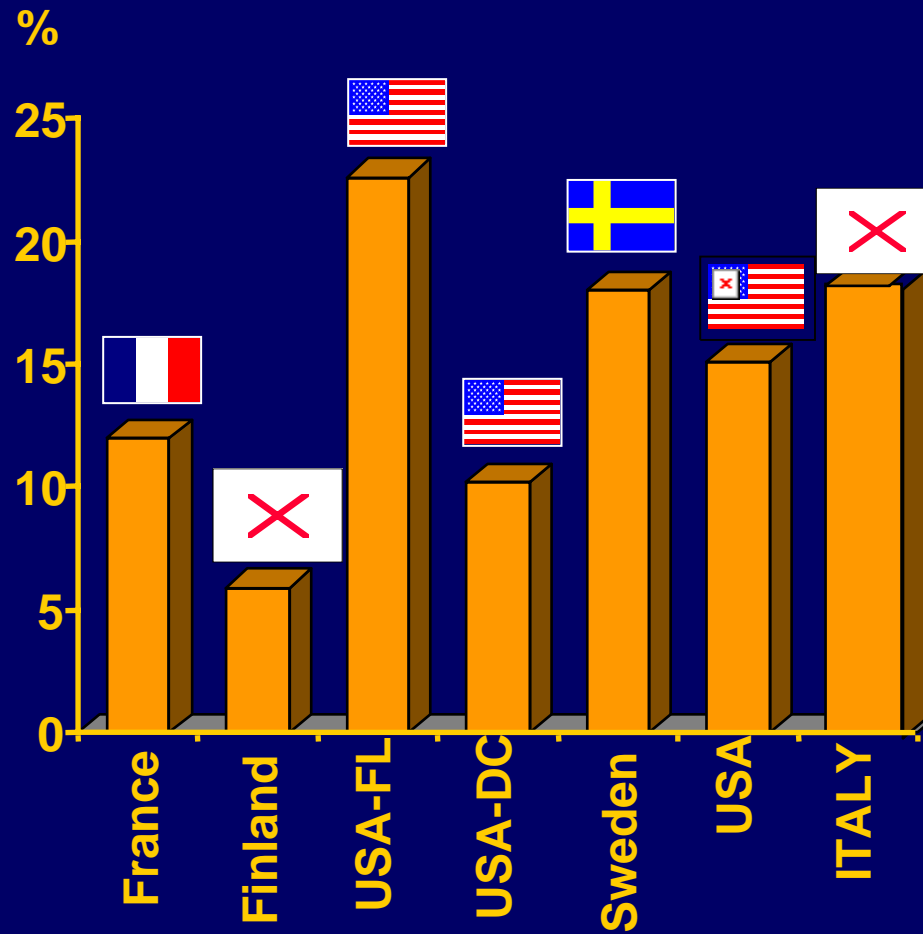
Study site	Total births	Cause of early-onset sepsis	No. Of cases (rate per 1,000 live births)					p-value	
			<u>1982 - 1987</u>		<u>1988 - 1993</u>				
Illinois (1 hospital) (94)	61,498	E. Coli	12 (0.37)	18 (0.62)				NS*	
		E. Coli (among low-birth weight† infants)	2 (0.67)	8 (2.83)				0.05	
California (1 hospital) (95)	29,897		<b>1991</b>	<b>1992</b>	<b>1993</b>	<b>1994</b>	<b>1995</b>	<b>1996</b>	
		GBS	5 (0.93)	3 (0.6)	2 (0.41)	2 (0.41)	2 (0.42)	1 (0.21)	NS
		Non-GBS	3 (0.56)	4 (0.8)	3 (0.61)	4 (0.81)	5 (1.04)	8 (1.65)	NS
		E. Coli	0 (0)	1 (0.2)	1 (0.2)	2 (0.41)	2 (0.42)	5 (1.03)	0.001
Illinois (1 hospital) (64)	20,981		<u>1992 - 1996</u>		<u>1997</u>				
		GBS	30 (1.7)	0 (0)				0.02	
		All causes	-§ (2.7)	- (2.1)				NS	
	All gram negative	5 (0.29)	5 (1.3)				0.05		

\* NS= not statistically significant; † Low birth weight defined as 1501-2500g; § Data not available

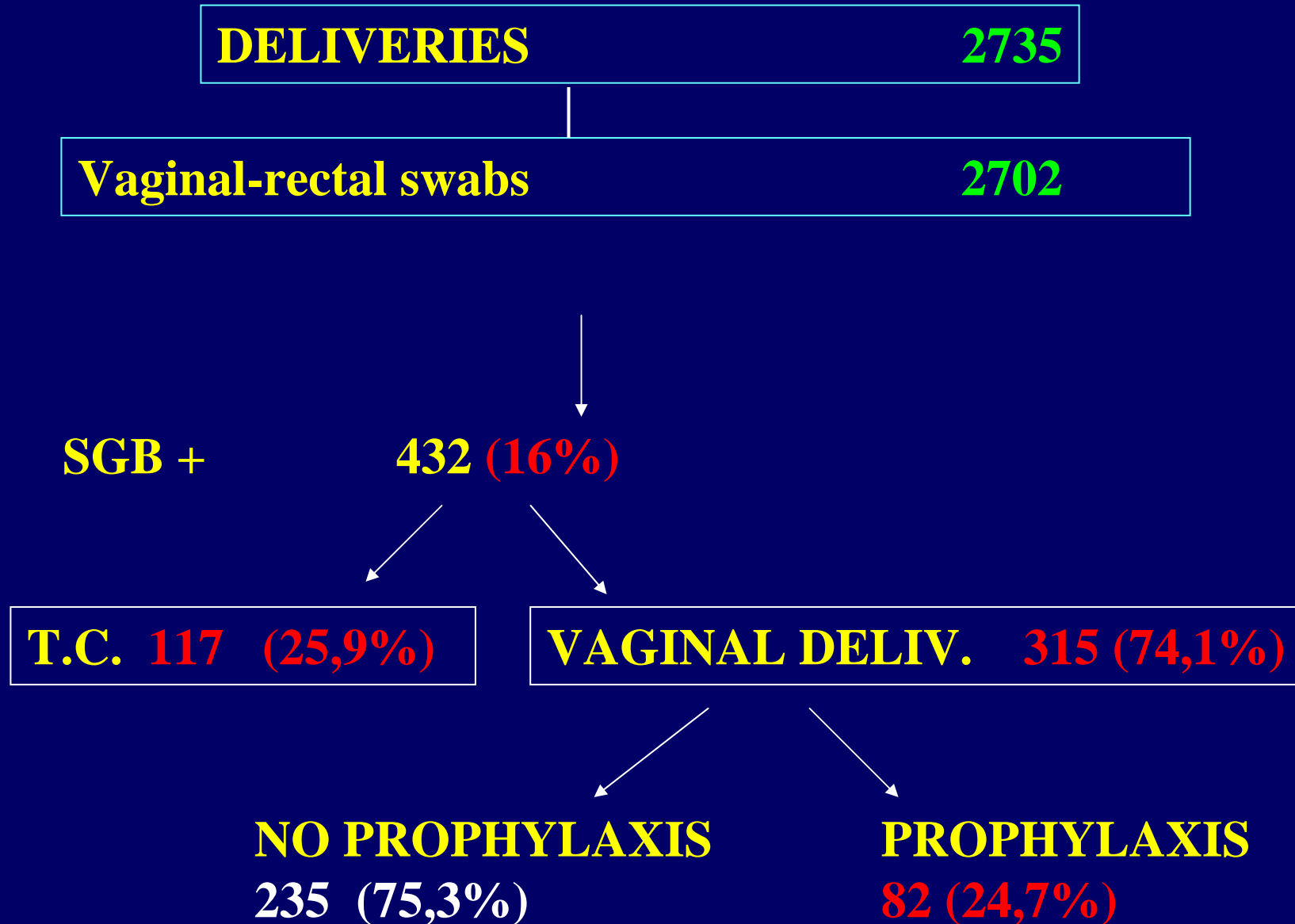
Selected neonatal morbidities among cases with early onset sepsis caused by GBS and E Coli

<i>Variable</i>	<i>GBS cases</i>	<i>E Coli cases</i>
Septicemia	56,7	85.3*
Pneumonia	18.3	9.1
Seizure	3.4	21.9
Acidosis	30.5	30.5
IVH	3.4	12.5
Mech ventil	13.6	53.1*

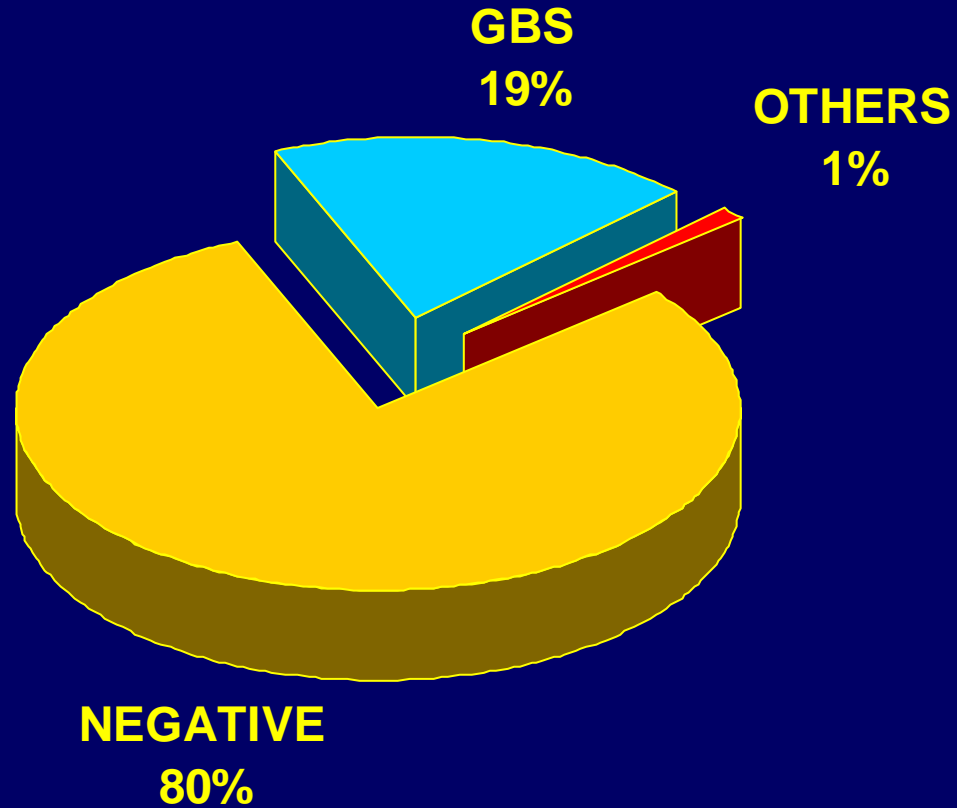
# PREVALENCE OF VAGINAL GBS CARRIERS



# UNIVERSAL SCREENING PLUS ANTIBIOTIC PROPHYLAXIS (18 months)

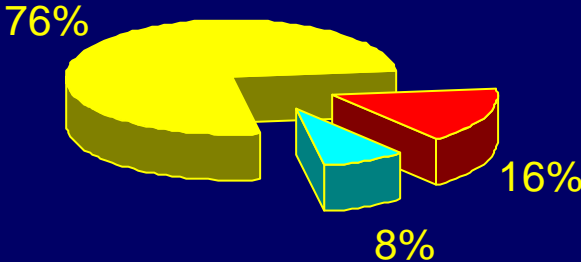


# VAGINAL SWAB AT 37 WEEKS AND PARTURITION



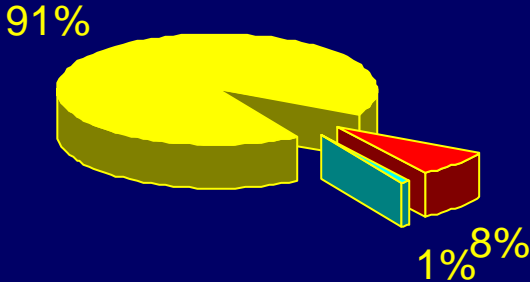
# DELIVERY ROUTE AND NEONATAL TRANSMISSION OF SGB AND E.COLI

### VAGINAL DELIVERY



■ NEGATIVI ■ SGB ■ E.COLI

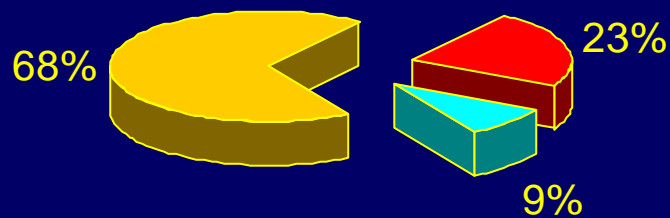
### CESAREAN SECTION



■ NEGATIVI ■ SGB ■ E.COLI

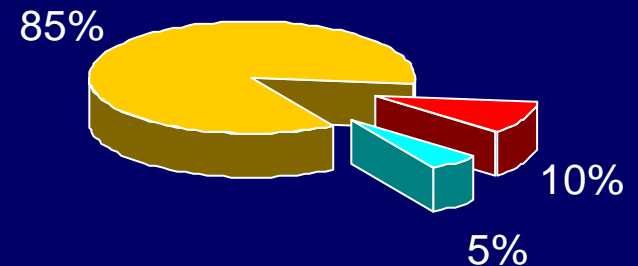
# NEONATAL COLONISATION with SGB and E.Coli with and without INTRA-PARTUM PROPHYLAXIS (vaginal del.)

## NO PROPHYLAXIS



■ NEGATIVI ■ SGB ■ E.COLI

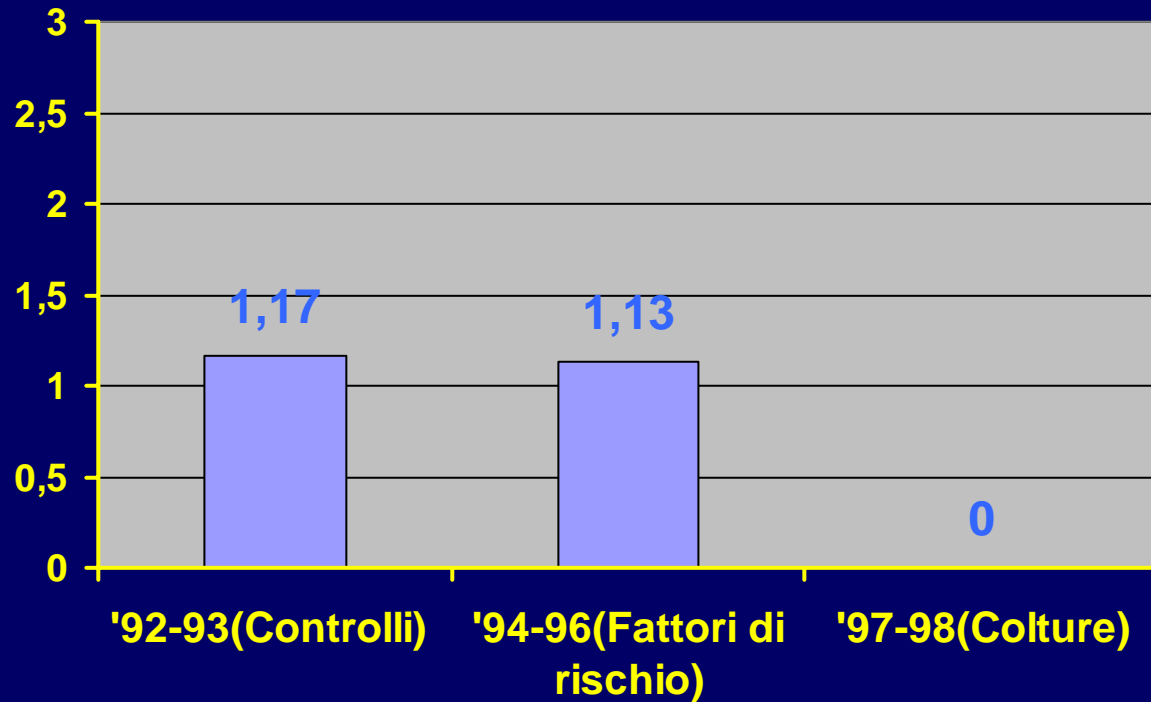
## PROPHYLAXIS



■ NEGATIVI ■ SGB ■ E.COLI

# INCIDENCE OF EARLY ONSET GBS DISEASE, SEPSIS AND MENINGITIS, ACCORDING TO SCREENING/PROPHYLAXIS

Tassi di infezioni  
invasive ad esordio  
precoce da SGB per  
1.000 nati



-----N.S.----- p =0.001-----

-----p=0.001-----

# ALTERNATIVE TREATMENT

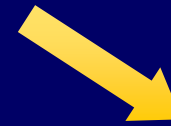
## VAGINAL-RECTAL POSITIVE CULTURE AND CLORHEXIDINE TREATMENT : ISOLATION OF MICROORGANISMS

<b>SPECIES</b>	<b>3rd DAY</b>	<b>10th DAY</b>
<b>Streptococcus B</b>	<b>50.0</b>	<b>18.6</b>
<b>Escherichia coli</b>	<b>43.8</b>	<b>10.0</b>
<b>ALL</b>	<b>46.7</b>	<b>15.0</b>
pH 4.83 ± 0.28	4.52 ± 0.25	4.22 ± 0.29

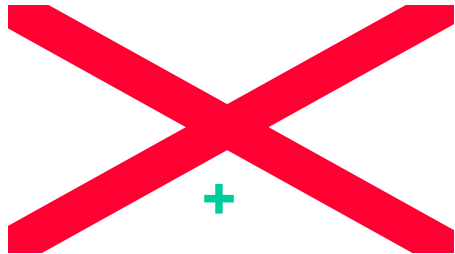
**POSITIVE ANTEPARTUM (35-37 wks) SWABS**  
**Randomization (odd/even records)**  
**244 CASES**



**Intrapartum prophylaxis**



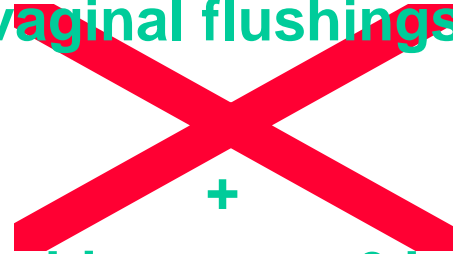
**2 g Ampicillin i.v. at admission**



**+**

**1 g i.m. every 6 hrs until delivery**

**140 ml Chlorhexidine (0.2%)  
(vaginal flushings)**



**+**

**One flushing every 6 hrs until  
delivery**

# LABOR FEATURES

	AMP (108 cases)	CLX (109 cases)
MATERNAL TEMPERATURE >38°C	3 (2.7)	1 (0.9)
LEUKOCYTES > 12.000/mm <sup>3</sup>	12 (11.1)	12 (11)
ROM > 18 hrs	21 (19.4)	17 (15.6)
LABOR > 8 hrs	87 (80.5)	69 (63.3)

Percentage in brackets

	Rate of <b>GBS</b> colonization	Rate of <b>E.Coli</b> colonization
<b>Overall rate of colonization</b>	13.8%	4.6%
<b>Women treated with Ampicillin (n=108)</b>	12.4%	7.4%
<b>Women treated with Chlorhexidine (n=109)</b>	15.6%	1.8%

P= 0.049

- No local or systemic undesired effects were recorded.
- Clinical features such as maternal age, weeks at delivery, labour more than 8 hrs, ROM at entry, maternal leukocytosis, birth-weight and Apgar score of negative and colonized newborns were similar.

# CLINICAL FEATURES OF INFECTED (GBS) NEONATES

	NEGATIVE (187 cases)	POSITIVE (30 cases)
MATERNAL AGE (years)	29.8 ± 4.1	30.2 ± 3.9
WEEKS AT DELIVERY	39.6 ± 1.3	39.8 ± 1.2
ROM > 18 hrs	6.8 %	6.4 %
LABOR > 8 hrs	18 %	26 %
MATERNAL LEUKOCYTES > 12.000/mm <sup>3</sup>	4.9 %	13.2 %
BIRTHWEIGHT (grams)	3388 ± 427	3503 ± 425
1-min APGAR	8.3 ± 1.3	8.3 ± 0.8
5-min APGAR	9.6 ± 0.9	9.7 ± 0.5

# POSITIVE SWABS FOR GBS AND E. COLI IN DIFFERENT NEONATAL SITES.

SITE	Neonatal swabs positive for GBS		Neonatal swabs positive for E. COLI	
	AMP	CLX	AMP	CLX
<del>Ear</del>	<del>12 (11.1)</del>	<del>14 (12.8)</del>	<del>6 (5.6)</del>	<del>2 (1.8)</del>
<del>Nasal</del>	<del>6 (5.55)</del>	<del>7 (6.4)</del>	<del>0</del>	<del>0</del>
<del>Gastric juice</del>	<del>2 (1.8)</del>	<del>3 (2.7)</del>	<del>2 (1.8)</del>	<del>0</del>
<del>At any site</del>	<del>13 (12)</del>	<del>17 (15.6)</del>	<del>8 (7.4)</del>	<del>2 (1.8)*</del>

Percentage in brackets

\* p=0.049

A.J.O.G. 180: S84, 1999

J.Mat.Fet.Neonat. Med. 11: 84-88, 2002

# SGB treatment with clorexidine 0.5% vaginal gel

- 30 pregnant patients enrolled consecutively with vaginal-cervical and/or urethral-rectal positivity to GBS
- GA varied between 14 and 32 wks
- Patients never treated before nor rec antibiotics
- Microb specimens collected at 5<sup>th</sup> day of therapy, 1 and 10 days after the end of therapy
- Microb evaluation performed by same laboratory

# RESULTS

- 27 out of 30 patients resulted negative at 1 and 10 days after therapy
- 1 patient resulted negative at 1 but positive at 10 days after therapy
- 2 patients resulted positive either at 1 and 10 days after therapy
- All patients except 1 resulted negative at the 5<sup>th</sup> day of therapy

# COMMENTS

- Topic therapy with chlorexidine 0.5% is efficacious in > 90% of cases at any stage of pregnancy
- Topic therapy is already efficacious at 5th day of treatment
- Patients' compliance resulted excellent with vaginal gel
- Topic therapy should be considered a valid and reliable alternative to parenteral therapy for SGB treatment in pregnancy

# ASSESSMENT

# WHO

**Since no combinations**

**of clinical and demographic information**

**could identify a subset of women whose screening**

**would identify the majority of carriers,**

**the screening programs should be applied**

**universally to all pregnant women.**

**SCREENING IS WORTHWHILE!**

# WHEN

**MICROBIOLOGICAL SCREENING IS  
THE PREFERRED APPROACH**

**Vaginal (and rectal) cultures  
should be performed  
from 35 to 37 weeks gestation.**

**The samples must be labeled  
“GBS detection”.**

# HOW

**Three different technical methods could be employed.**

**According to CDC recommendations, swabs should be placed in selective broth medium, then subcultured in sheep blood agar plates.**

**The organism suggestive of GBS should be identified by antigen detection or by CAMP test.**

**Susceptibility to erythromycin and clindamycin should be verified only for penicillin-allergic patients. In alternative, after culture in selective medium, the samples could be plated on GBS (Islam) or Granada agar plates, allowing direct GBS identification by detection of carotenoid pigment production.**

**Strains that do not produce pigment require further GBS identification.**

**Finally, swabs can be directly cultured in Instant Granada medium tubes, with identification within 18 hours.**

# PROPHYLAXIS

Intrapartum prophylaxis should be given

- to all pregnant women identified as GBS carriers.

In addition, prophylaxis should be given

- to all women with preterm onset of labor (<37 wks) and unknown GBS colonization status;
- to all women with GBS isolated from the urine in any concentration during their current pregnancy;
- to women who have previously given birth to an infant with GBS disease;
- to all women with unknown GBS colonization status

# - Conclusion -

**GBS SCREENING SHOULD BE ROUTINE PART OF ANTENATAL CARE**

**It would be extremely helpful to have a low cost, easy-to-use method for the disinfection of the birth canal, in order to prevent peripartal transmission of infecting agents (HIV included).**

**Chlorhexidine vaginal gel seems to fulfil this need.**

**SAVE THE DATE**

8<sup>th</sup>



World Congress  
of Perinatal Medicine



WCPM

**Florence (Italy), 9-13 September 2007**

**THANK YOU**

**GRAZIE**

**G.C. Di Renzo**