Is PPROM latency influenced by single vs multiple agent antibiotic prophylaxis in known GBS positive women delivering preterm?

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Background

- Preterm Prelabour Rupture of Membranes (PPROM) is the rupture of membrane of the amniotic sac, in the absence of labor, occurring at < 37 weeks GA.
- Occurs in 2-3.5% of all pregnancies in Canada.
- PPROM is the most common cause of preterm birth.

Yudin et al. JOGC, 2009; 233: 863.

Background

- It has been previously demonstrated that management PPROM with either ampicillin and erythromycin or erythromycin alone prolongs the latency period reducing neonatal morbidity associated with prematurity.
- Previous literature suggests that GBS is an important consideration for PPROM management.
- There are no specific antibiotic recommendations for GBS in the setting of PPROM.

Kenyon et al. Lancet. 2001; 357:979.
Mercer et al. JAMA. 1997 Sep 24;278(12):989.
Gilbert et al. BJOG, 2005; 112: 830.

Background

- Reported resistance amongst GBS isolates for erythromycin have been found to be between 25-32%.
- Erythromycin and Ampicillin are no longer suitable second line agents for GBS prophylaxis due to increasing resistance.
- **Is a single agent therapy suboptimal for the management of PPROM?**

Hypothesis

- Women with PPROM and GBS positive urine or vaginal/rectal culture, delivering preterm, may benefit from the administration of multiple agent antibiotic prophylaxis for the management of PPROM, compared to single agent alone.

Objectives

- Review antibiotic administration for GBS prophylaxis in the setting of PPROM at the IWK Health Centre.

- Primary outcome
  - Determine if there is a statistically significant difference in latency between GBS positive women with PPROM treated with single agent antibiotic prophylaxis alone versus multiple antibiotic prophylaxis protocols.

- Secondary outcome
  - Determine if there are statistically significant differences in the incidence of composite neonatal infectious outcomes between treatment exposures.

Methodology

- Retrospective population based cohort study
- Approval was received from the Joint Data Access Committee-Reproductive Care Program Database Access Committee and the IWK REB.

Methodology

Inclusion Criteria

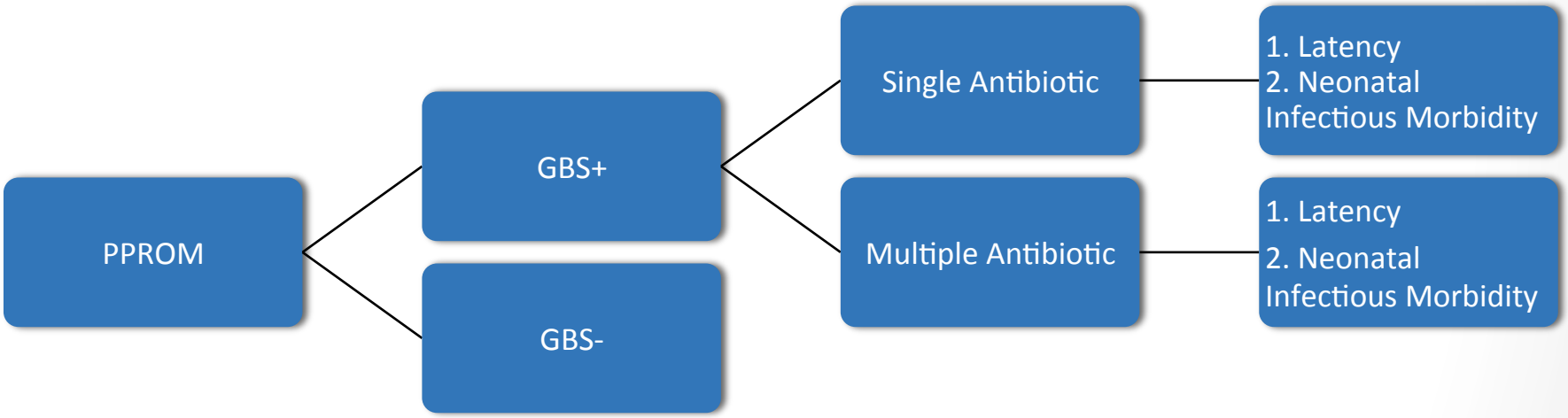
- 1988-2011
- Preterm IWK delivery
- Nova Scotia Resident
- PPROM at $\geq 24^{0} \leq 36^{6}$ gestation
- GBS status known

Exclusion Criteria

- Multiple gestations
- Major Congenital anomalies
- Pre-existing hypertension or diabetes
- Preeclampsia, HELLP, eclampsia
- Gestational DM on insulin
- Recent antibiotic use

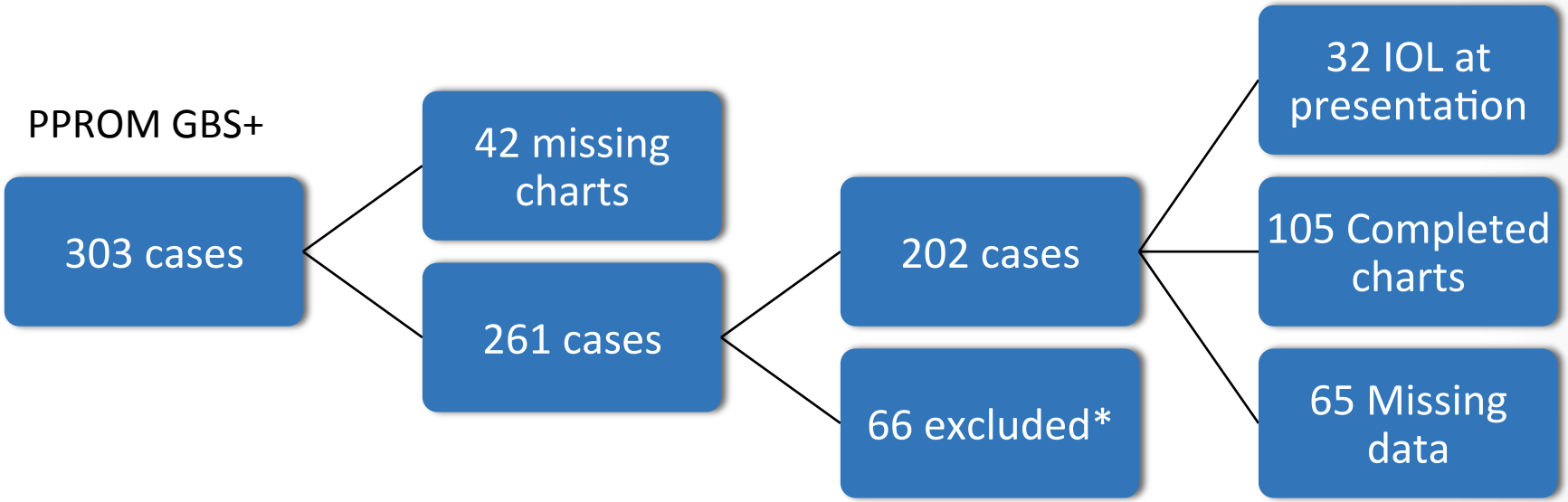
Methodology

Retrospective Cohort Population-based Study



Nova Scotia Atlee Perinatal Database ⟹ Chart Review ⟹ Data Linkage

Methodology



***Reason for Exclusion:**
17 = GBS – or unknown
23 = Labor on arrival
7 = >36 c/s; repeat or planned (HSV; malpresentation)
16 = >36[6]
1 = Previable PPROM
1 = 2wk Hx PPROM at presentation
1 = abruption

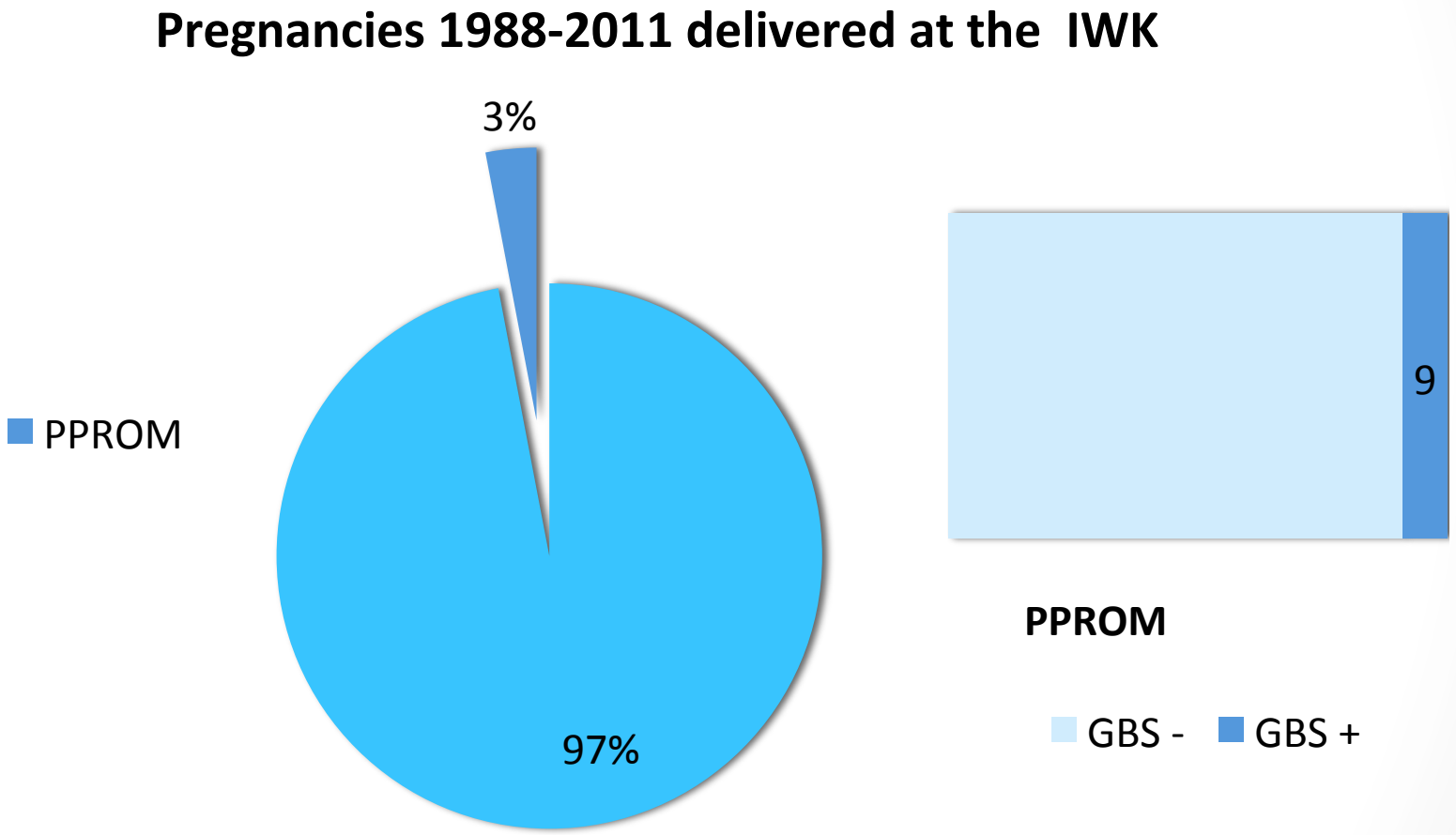
Methodology: Statistical Analysis

- The type of antibiotic PPROM prophylaxis used between 1988-2011 was summarized.
- Summary characteristics were compared using Chi-square analysis with significance <0.05.
- Comparisons in latency and adverse neonatal outcomes were made based on single vs multiple antibiotics administration.
- Logistic and linear regressions were used where appropriate to estimate adjusted odds ratios and 95% confidence intervals for all outcomes and to account for confounding variables.

Methodology: Statistical Analysis

- Potential confounding variables:
  - Maternal age
  - Gestational age at ruptured membranes
  - Smoking
  - Nulliparity
  - Low socioeconomic status - as defined by quintiles of neighbourhood income per single person equivalent (QAIPPE)
  - Maternal weight at delivery
  - Steroid administration
  - Spontaneous onset of labour

Results

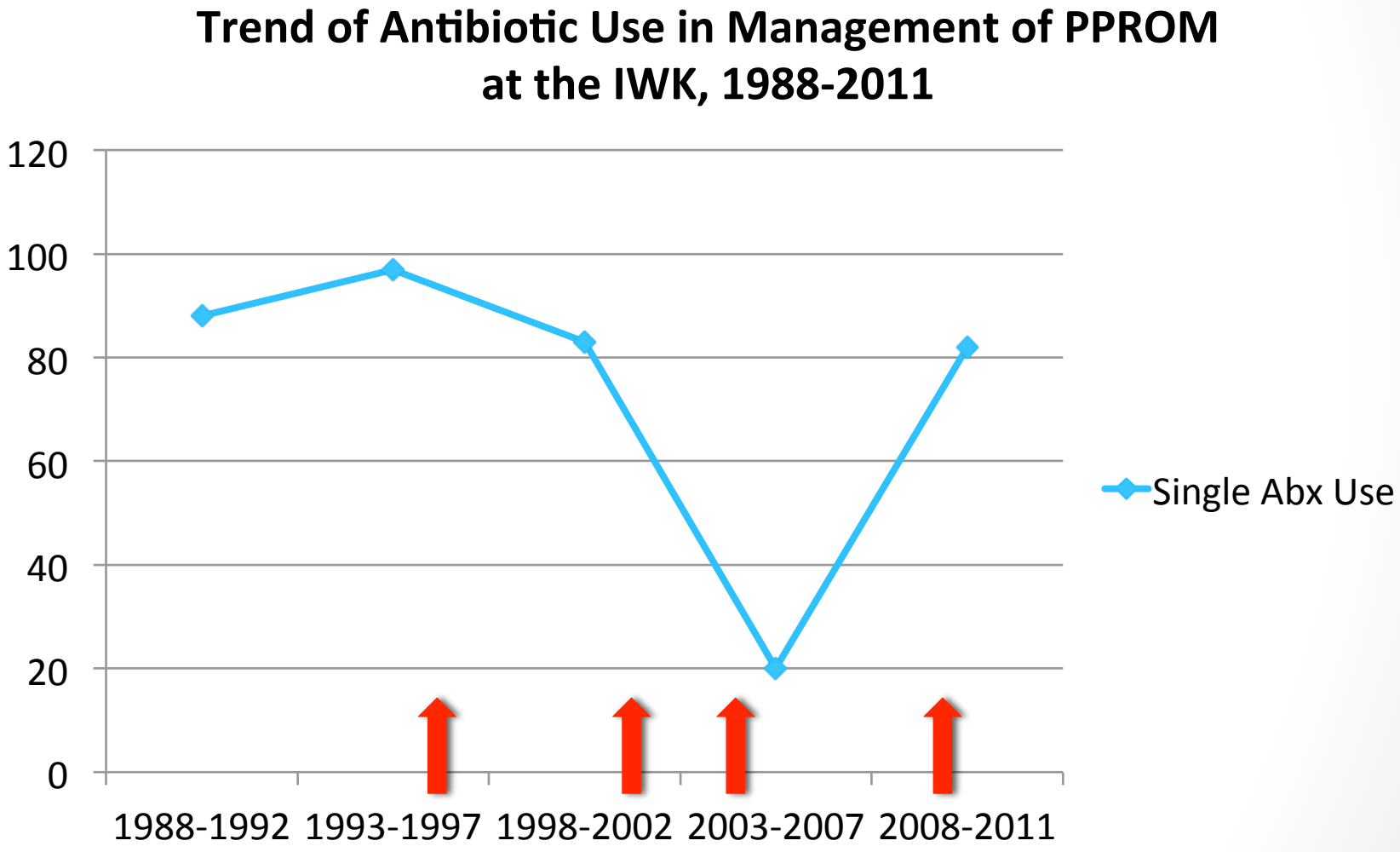

Pregnancies 1988-2011 delivered at the IWK
3%
PPROM
97%
9
PPROM
GBS -
GBS +

Results

Type of antibiotics used in PPROM with known GBS positive status

Antibiotic	Number (%)
None	24 (22)
Ampicillin	44 (40)
Erythromycin	18 ((17)
Clindamycin	1 (1)
Penicillin	1 (1)
Ampicillin/Erythromycin	14 (13)
Ampicillin/Penicillin	1 (1)
Erythromycin/Clindamycin	4(4)
Ampicillin/Erythromycin/Penicillin	2 (2)

Results


Trend of Antibiotic Use in Management of PPROM at the IWK, 1988-2011
120
100
80
60
40
20
0
1988-1992
1993-1997
1998-2002
2003-2007
2008-2011
Single Abx Use

Results

Summary Characteristics

	Single Antibiotic n=67	Multiple antibiotic n=18	P value
Mean maternal age, y (SD)	29.3 (5.8)	27.7 (5.9)	.30
Nulliparous (%)	40 (60)	7 (39)	.12
Mean prepregnancy weight, kg (SD)	66.8 (19.6)	70.2 (15.5)	.57
Smoking (%)	27 (40)	8 (47)	.61
Low SES (%)	40 (60)	9 (52)	.61
Previous CS (%)	8 (12)	5 (28)	.10
Steroids (%)	35 (52)	16 (89)	.005
Other Abx exposure (%)	12 (18)	<5 (<27.8)	1.0
Chorio (%)	12 (18)	0 (0)	.06
Intrapartum Abx exposure (%)	54 (81)	13 (72)	.52
Spontaneous labour (%)	46 (69)	8 (44)	.06
CS in current pregnancy (%)	12 (18)	10 (56)	.001
Mean GA at PPROM, wk (SD)	32.5 (3.1)	30.4 (4.1)	.03
Mean GA at delivery, wk (SD)	33.5 (2.6)	32.6 (2.5)	.22

Results

Univariate and logistic and linear regressions

	Single Antibiotic n=64	Multiple Antibiotics n=17	OR Mean difference	aOR*
Latency > 48h (%)	44 (69)	14 (82)	2.1 (0.5-12.7)	2.1 (0.5-12.7)
Mean latency, d (SD)	7.4 (9.7)	17.0 (29.0)	9.5, p=.03	3.5, p=.25
Neonatal sepsis (%)	11 (16)	< 5 (<29)	3.3 (0.4-152)	undefined

***Adjusted for GA at ROM**

Discussion

- Evaluation of latency and neonatal infectious morbidity with PPROM delivering preterm in this selected population demonstrated:
  - Low numbers of documented GBS positive urine, vaginal/rectal or newborn cultures in women with PPROM delivering preterm.
  - Significant differences were seen in:
    - Antenatal steroid administration
    - Caesarean section in current pregnancy
    - Mean gestational age at PPROM

Discussion

- There was a wide variation in practice in antibiotic administration for latency in women with PPROM and documented maternal and/or newborn GBS positive status.
  - 22% of women did not receive antibiotics

- The type of antibiotic regimen did not influence either latency with PPROM and GBS positive culture or rates of neonatal sepsis.

Discussion

- The derived number of patients eligible for inclusion following the chart review was less than expected from the feasibility study.

- Post hoc power calculation showed that our study had a 16.3% power to detect a statistically significant difference between cohorts with respect to change in latency time.

Limitations

- Absence of large numbers of women with PPROM and known GBS positive status.
- We considered all pregnancies with known GBS positive cultures, including those from the newborn.
- The duration of the study period.
  - 24 years of data
- Limited by variables in the database and information on type of antibiotics retrievable from the chart review.

Future Directions

- The 2013 SOGC recommendations highlight the need for consistent management of women with PPROM, including documenting GBS status early, administering appropriate antibiotics, and documenting sensitivities with penicillin allergies.
  - Ampicillin or erythromycin are no longer recommended as first line or second line treatment for GBS prophylaxis due to bacterial resistance.

- Ongoing evaluation of pregnancy duration and serious neonatal outcomes such as sepsis in our centre is essential given this change in recommendation.

Money, DM and Allen, VM, 2013

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IWK Health Centre

Research

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Feasibility Study

- Preliminary NSAPD data:
  - 1200 women with PPROM 2003-2010
  - 79 estimated to be GBS positive
    - 38 estimated to receive single antibiotic
    - 75% of remaining 41 estimated to have received multiple antibiotics
- With latency measured as a dichotomous variable
  - Assumed latency > 48 hours incidence of 5% among single antibiotics
  - Assumed latency > 48 hours incidence of 30% among multiple antibiotics
  - α=.05
  - Power = 70.5%

Grable et. al., 1996.