Root Cause Analysis of the Carey/Klebaroff Study: Confirmation of Imperatives to Readdress Prevention of Infection/Inflammation-Caused Preterm Birth (I/I-PTB)

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ABSTRACT

Objective: The C/K paper of 2000 had powerful negative influence among practitioners in suggesting that "antibiotics cannot reduce PTB." Our objective was to review this study to understand why it remains an influential negative "outlier" among similar studies using "Quality" and "Root Cause"-informed analyses.
Methods: We reviewed relevant, comparative controlled trials and narratives including Cochrane Reviews and used those to inform Quality-based analysis.
Results: 1) Close analysis suggests that Lamont's editorial criticisms in which he concluded " 'wrong' design, drug, timing and interpretation/conclusions" (paraphrased) are partially correct as a) the authors C/K have subsequently publically noted, the study was conceived in the 1980's and was dated in concept (identifiable and reliably treatable vaginal infections [BV, TV]) cause PTB; and that b) treatment later in pregnancy, up to 28 weeks gestation, is effective;, c) using an unevaluated empiric dose of metronidazole; d) which was hypothesized to eliminate/ameliorate I/I, pathophysiologic mechanisms; and e) and that no further RCTs are indicated.
2) Conversely, subsequent controlled trials show that a) early-pregnancy (<20 gestational week); and b) comprehensive treatment of prevalent lower reproductive tract infections (LRTIs) of unselected population; which c) include use of a clindamycin-related antimicrobials (i.e., those with anti-inflammatory, anti-virulence factor, anti-mycoplasmal effects) for treatment of bacterial vaginosis (BV) are consistently effective in reducing PTB (<32,<37 week gestation) and possibly "late miscarriage" (LM).

Conclusion: There is sufficient evidence to readdress the problem of PTB mediated by I/I with large, sufficiently powered, biologically coherent, scientifically designed, NIH funded, and cogently designed trials, in susceptible US populations.

BACKGROUND

- PTD is a leading cause of preventable morbidity, mortality, CNS delays/ deficits, and lost income/productivity
- Abnormal vaginal microflora associated with late miscarriage (LM), PTB/ LBW/pPROM worldwide
- Mixed results demonstrated in studies with differing designs, diagnostic methods, populations, and treatment approaches

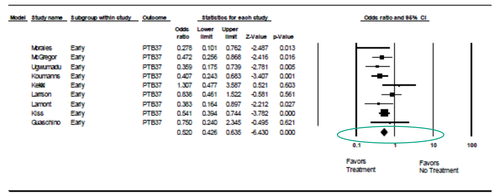
GOALS

- Systematically review and analyze available studies focusing on reducing BV/AVF associated PTB
- Examine original studies for unappreciated biologic (growth/ development, microbiologic), timing of diagnosis, treatment, F/U, and patient selection
- Evaluate possible effects of these programmatic components using meta-analysis to identify treatment benefits or harms.
- Identify possible treatment strategies that were clinically effective, not associated with harm, clinically practicable in differing settings, and KISS approaches

METHODS

- **Systematic review** of published medical literature on Medline, PubMed, & Cochrane Library for1980-2011 using the keywords: Bacterial vaginosis, treatment, antibiotics, preterm birth, late miscarriage, pPROM; Internal files from professional meeting abstracts were also searched for additional studies, then data bases were search for these specific studies
- **Studies Inclusion Criteria:**
  - Comparison group either placebo or untreated women with symptomatic or asymptomatic BV/AVF
  - Reported gestational age at assessment and treatment
  - Study enrollment prior to onset of labor or ROM
  - Reported number with birth prior to 37 wks gestation (Primary outcome)
- **Study**
  - 195 Studies identified including 20 treatment trials
  - Excluded studies (N=4):
    - 1- data were included in another multi-center study
    - 3- only sub-populations of women were included
  - Included studies (N=16):
    - 10 DB-RCT
    - 3- RCT (treatment vs. non-treatment)
    - 3-quasi-experimental (non-treatment observation control)
  - Meta-analysis of retrieved data performed using Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ)
  - Random effects models examined to account for variance between studies as well as within studies
  - Heterogeneity examined using I^2 and Tau^2 statistics
    - I^2 estimates amount of variation between studies due to effect differences rather than random error (low heterogeneity = I^2~ 25; medium heterogeneity = I^2~ 50; high heterogeneity = I^2~ 75)

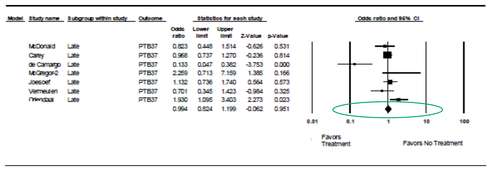
Reduction of Preterm Birth by Early Screening and Treatment for Bacterial Vaginosis (≤ 20 wks)



Plot shows- Low level of heterogeneity between studies (I^2 =20.5)

	OR	Lower	Upper	p-Value
Random Effects Model	0.52	0.41	0.66	0.000

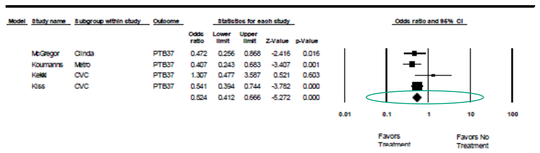
Late Screening and Treatment for Bacterial Vaginosis



Plot shows- High level of heterogeneity between studies (I^2 = 74)

	OR	Lower	Upper	p-Value
Random Effects Model	0.924	0.603	1.416	0.72

Comprehensive & Early Screening and Treatment for Prevalent Urine and Reproductive Tract Infections



Plot shows a Moderate level of heterogeneity between studies (I^2 =28.9)

	OR	Lower	Upper	p-Value
Random Effects Model	0.528	0.39	0.72	0.000

RESULTS

Treatment ≤ 20 wks gestation (9 studies) significantly reduced PTB < 37 wks
OR 0.52 (95% CI 0.41-0.66)
Treatment > 20 wks gestation (7 studies) was not associated with reduced PTB
OR 0.92 (95% CI 0.60-1.41)
Comprehensive Treatments ≤ 20 wks gestation (4 studies) significantly reduced PTB < 37 wks
OR 0.52 (95% CI 0.39-0.72)
Similar to studied that only examined BV
OR 0.5 (95% CI 0.32-0.77)

DISCUSSION

STRENGTHS & LIMITATIONS

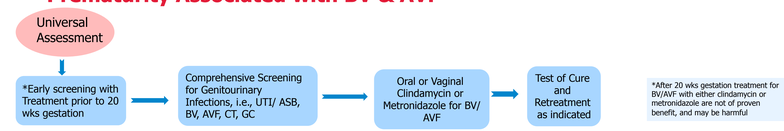
Threats to applicability

1. Meta-analysis
   a. Limited by original study quality
   b. Limited by number of studies & populations studied
   c. Subject to study selection bias
   d. Limited by analytical techniques
2. Heterogeneity
   a. No consistent design (Dx, Rx, TOC, Outcomes, 37 vs 34 wks, LM)
   b. Multiple populations (other prevalent causes of PTD, age, ethnicity, etc)
      i. NNS, NNT differ range 10-fold

STRENGTHS

1. Meta-analysis:
   a. Summarizes and integrates results from several studies
   b. Combination of smaller studies allows examination of outcomes that require larger samples sizes
   c. Suggest new studies needed
2. Conservative selection of studies and interpretation
3. Low I^2 (20.5%) suggesting relative low heterogeneity between studies
4. Cc
5. Consistent with other studies: Morency, Shaw, Cochrane, Canadian experts
6. MTX effective ≤ 20 wks gestation
7. Consistent with causality criteria "biologically plausible"
8. No harms noted
9. Proposed approach: screen & treat early (≤20 wks) /TOC and retreat
10. Inexpensive: easy, widely applicable, specificity vs sensitivity

Proposed Clinical Pathway to Reduce Risk of Prematurity Associated with BV & AVF



CONCLUSIONS

1. Biologically plausible and consistent with other studies
2. Early (≤ 20 wks) screening and prompt treatment with benefit
3. Comprehensive screening for common genitourinary infections ASB/UTI, BV, AVF, prevalent STIs is associated with benefits
4. CDC-recommended TOC and retreatment practices did not confer additional benefit
5. Clindamycin and MTZ comparably benefit with ≤ 20 wks
6. No studies evaluated vaginal MTZ
7. NNT varied widely 1: 10 to 1:80
8. Only Lamont's study calculated $'s saved and reduced admissions
9. Could not establish different benefits among different race/ethnic groups
10. No standardized approaches

RECOMMENDATIONS

1. **Screen &treat ALL women for abnormal flora/BV and common RTIs**
2. **Early ≤ 20 wks treatment preferred**
3. **Early Clindamycin (oral vs topical) most beneficial**
4. **Early Clindamycin and Metronidazole (prior PTB) both effective**
5. **Late Metronidazole effective in (A) Prior PTB and (B) San Paulo Population**
6. **Avoid late treatment with Clindamycin**
7. **"Screen, Treat, Prevent" for all prevalent abnormal genital microflora in all pregnant women at initial visit**
8. **"Home test in all pregnant women with vaginal pH testing weekly (U. Hoyme, et al)**

REFERENCES

Handout