



Perinatal
Outreach
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Partner

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Infections, Antibiotics and Preterm Labour

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PRETERM BIRTH remains a major obstetrical problem accounting for 70% of perinatal mortality and nearly half of long-term neurologic morbidity. Ten percent of all births are preterm, with the most serious illness and death in the 1-2% born before 32 weeks gestation and weighing less than 1500 grams. Although 20% of preterm births are secondary to inductions for maternal or fetal reasons, 80% are due to preterm premature rupture of membranes (PPROM) or spontaneous preterm labour [1].

Approximately one third of preterm deliveries are caused by subclinical or clinical upper genital tract infections. Bacteria ascends from the maternal genital tract into the uterus, causing an inflammatory response, and thereby inducing preterm labour [2]. Therefore, maternal genital tract infection and/or colonization may be one of the most important modifiable risk factors to decrease the rate of preterm labour.

PATHOGENESIS

Evidence gathered over the past 20 years demonstrates infection may cause 20-40% of preterm births. This evidence can be summarized as follows: 1) histologic chorioamnionitis is consistently increased in preterm births, 2) clinical infection is increased after preterm birth in both the newborn and the mother, 3) 10-15% of amniotic fluid cultures are positive in patients in preterm labour, 4) infection and inflammation cause cytokine and

prostaglandin production, and 5) antibiotics lower preterm birth in some trials [3].

Endotoxins and exotoxins are released by bacteria and invade the chorio-decidual space. This increases the production of cytokines, such as interleukin-1 (IL-1), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-alpha), and granulocyte colony stimulating factor (GCS-F). The increase in cytokines augments the production of prostaglandins, increases infiltration of neutrophils, which increase metalloproteases. The prostaglandins lead to myometrial contractions, while the metalloproteases ripen the cervix and weaken the chorioamnion, predisposing to rupture of membranes. These activities in concert lead to preterm birth [1].

(Cont'd)

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The most common organisms isolated from placental membranes among women with preterm birth include: *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Gardnerella vaginalis*, *E. coli*, Group B *Streptococcus*, *Peptostreptococcus* species, and *Bacteroides* species [1].

BACTERIAL VAGINOSIS

Bacterial vaginosis (BV) is not an infection per se, but an alteration in the endogenous vaginal flora. Lactobacillus, which normally resides in the vaginal tract, is replaced by *Gardnerella vaginalis*, *Mobiluncus* species, anaerobes, and genital mycoplasmas [4]. The prevalence of BV in pregnancy is approximately 10-20%; 50% of the time, these women are asymptomatic [5]. Early studies have found that those with BV in pregnancy have an increased risk of preterm labour, PPROM and preterm birth [6].

Several treatment trials demonstrate reductions in preterm birth among women with both symptomatic and asymptomatic BV during pregnancy. McGregor *et al* [7] and Morales *et al* [8] both demonstrated the risk of preterm birth reduced by 50% among women with BV who received oral antibiotics compared to untreated controls or placebos. Hauth *et al* [9] randomized women at risk for preterm birth to either metronidazole and erythromycin or dual placebos. Women with antibiotics had a reduction in preterm birth (49% to 31%) compared with women given placebos (p=0.006). In contrast, the largest trials studying treatment of asymptomatic BV during pregnancy were done by McDonald *et al* [10] and Carey *et al* [11], consisting of 879 women and 1953 women, respectively. They concluded that the treatment of asymptomatic bacterial vaginosis in pregnant women does not reduce the rate of preterm birth. A meta-analysis done by Leitich *et al* [12], involving 10 studies with results for 3969 patients, showed that antibiotic treatment did not decrease preterm birth in all patients combined (OR 0.83; 95% CI 0.57-1.21) or in high risk patients with previous preterm birth (OR 0.50; 95% CI 0.22-1.12).

In summary, in pregnant women with BV who are asymptomatic and at low risk of preterm birth, antibiotics do not decrease the risk of preterm birth [10, 11]. Universal screening of women at low risk without symptoms is not

recommended [10, 13]. For all pregnant women who are symptomatic, however, it is recommended to screen and treat all of these women. Treatment recommended by the Center for Disease Control (CDC) is metronidazole 250 mg TID or 500 mg BID for 7 days, or clindamycin 300 mg BID for 7 days [14]. Intravaginal treatment with clindamycin cream is not as effective as oral antibiotics [15].

In pregnant women who are asymptomatic for BV, but have had a previous preterm birth and are therefore at high risk for a second preterm birth, screening for bacterial vaginosis is an option, but not the standard of care, since there are numerous conflicting studies [8, 9, 11, 12]. The guidelines stated by the U.S. Preventive Services Task Force (USPSTF) state that evidence is insufficient to recommend for or against routinely screening high-risk pregnant women for BV [16]. The American College of Obstetrics & Gynecology (ACOG) states that there is no current data to support the use of BV screening strategies to prevent preterm birth [17]. At our centre, all women with previous preterm birth are screened for bacterial vaginosis, and are treated if the results are positive.

SEXUALLY TRANSMITTED DISEASES

a) Trichomonas vaginalis

The Vaginal Infections and Prematurity Study demonstrated that pregnant women with *Trichomonas vaginalis* have a 30% higher risk of having a preterm birth, a 2-fold risk of stillbirth or neonatal death, and PPROM [18]. The treatment for *T. vaginalis* is metronidazole 2 g PO x 1 dose [14].

Klebanoff *et al* [19] randomized 617 women with asymptomatic *T. vaginalis* to treatment with metronidazole or placebo and found that treatment with antibiotics did not prevent preterm delivery. Therefore, routine screening and treatment of asymptomatic pregnant women for *T. vaginalis* is not recommended.

b) Chlamydia & Gonorrhoea

The primary rationale for screening/treatment of these two diseases is to prevent vertical transmission of serious systemic and eye infections of the neonate. There is also an increased risk of preterm birth with both of these infections [20].

Routine screening for chlamydia and gonorrhoea is recommended. If positive, treatment should consist as follows: for chlamydia, erythromycin 500 mg qid x 7 days, amoxicillin 500mg tid x 7 days or azithromycin 1 g po x 1. For gonorrhoea, ceftriaxone 125 mg IM x 1, cefixime 400 mg po x1 or spectinomycin 2 g IM x 1 [21].

UREAPLASMA UREALYTICUM

In previous reports, *U. Urealyticum* has been isolated from the placenta, newborn infant, and genital cultures at delivery, and therefore associated with preterm birth and low birth weight [22]. However, these studies did not control for other organisms that may be associated with *U. Urealyticum*. Carey *et al* [23] controlled for the presence of other organisms in 4934 women, and found there was no association between maternal genital tract colonization with *U. Urealyticum* and low birthweight, preterm birth or PPRM. In addition, a multicentre randomized trial of >900 patients with *U. Urealyticum* (excluding those with *C. trachomatis* and GBS) found there was no impact on adverse pregnancy outcomes when treated with erythromycin vs placebo [24].

Therefore, *U. urealyticum* is part of the vaginal microflora in many women and is not associated with an increased risk of preterm birth [1]. It is recommended to not screen for or treat *U. urealyticum*.

ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria occurs in 3-10% of all pregnant women and is defined as the isolation of >100,000 CFU of a single organism/ml in a midstream voided specimen in someone without urinary tract infection symptoms. If untreated, 30-50% of these women will develop pyelonephritis, and the risk of delivery during an episode of acute pyelonephritis is approximately 30% [4].

Two meta-analyses [25,26] have shown that antibiotic treatment of asymptomatic bacteriuria is associated with a reduction in the incidence of preterm delivery or low birthweight babies. Therefore, patients should be screened and treated to prevent pyelonephritis and preterm birth associated with asymptomatic bacteriuria. *E. Coli* is isolated in >80% of cases, though other gram negative rods (*Klebsiella*, *Proteus*) or gram

positive cocci (enterococci, GBS) may be found. Treatment should be as follows: nitrofurantoin 100 mg po bid, amoxicillin 500 mg po tid, cefalexin 250mg po qid or sulfonamide 500 mg po qid [21]. A 3-7 day course of antibiotics is sufficient. Antibiotic resistance to amoxicillin and sulfonamide can be substantial, however, and one should establish if the isolate is susceptible. Sulfa drugs in the 3rd trimester should not be used because of the theoretical risk of kernicterus [27]. In addition, if a patient has bacteriuria with Group B streptococcus (GBS), any degree of colonization should be treated when diagnosed. These patients require GBS prophylaxis intrapartum, regardless of the results of the vaginal-rectal culture [3, 37].

ANTIBIOTICS FOR PRETERM LABOUR

Studies have looked at the use of antibiotics to inhibit preterm labour with intact membranes. The largest randomized trial is ORACLE II [28] where 6295 women in spontaneous preterm labour and intact membranes, with no evidence of clinical infection were randomly assigned to different antibiotic regimens vs placebo for 10 days or until delivery. Results demonstrated there was no prolongation of pregnancy, no differences in neonatal health and therefore no benefits by any of the antibiotic regimens. This study concluded that antibiotics should not be routinely prescribed for women in spontaneous preterm labour without evidence of clinical infection. The same results were obtained by King *et al* [29] in their meta-analysis in the Cochrane Review, consisting of 11 trials, with 7429 women in preterm labour with intact membranes.

Overall, there is no benefit for prophylactic antibiotics in preterm labour with intact membranes. Treatment of women with preterm labour with antibiotics to reduce preterm labour is not recommended [30]. Antibiotics should only be used intrapartum for GBS prophylaxis.(37)

PRETERM PREMATURE RUPTURE OF MEMBRANES (PPROM)

The correlation between PPRM and intrauterine microbial invasion is well established. Studies have found associations between PPRM and positive amniotic fluid cultures, clinical chorioamnionitis and histological chorioamnionitis [31]. Ascending

infection from the lower genital tract also plays a role. The goals of antimicrobials are to treat existing subclinical intrauterine infection, and to prevent ascending infection after the protective membrane barrier has been disrupted.

Mercer *et al*, in the NICHD multicentre trial [32], studied 614 women with PPROM between 24 and 32 weeks gestation, who were randomized between antibiotic treatment (ampicillin IV 2g IV q 6hrs and erythromycin 250mg IV q 6 hrs x 48 hrs, followed by oral amoxicillin 250mg q8hrs and erythromycin base 333mg q8hrs x 5 days) vs placebo. Results showed the antibiotic treated group had a significant prolongation of pregnancy by 6.1 days vs 2.9 days ($p<0.001$), in addition to decreased respiratory distress ($p=0.04$), decreased necrotizing enterocolitis ($p=0.03$), mortality, sepsis and intraventricular hemorrhage ($p=0.04$). This study concluded that those with PPROM between 24 and 32 weeks will benefit from antibiotics to reduce morbidity and prolong pregnancy.

This was further demonstrated in ORACLE I [33], where 4826 women with PPROM <37 wks gestation were randomly assigned to erythromycin 250mg qid, co-amoxiclav 325 mg qid, both antibiotics or placebo for 10 days or until delivery. In the erythromycin group, there was a significant decreased likelihood of delivery in 48 hrs ($p=0.004$) and 7 days ($p=0.05$), and a significant decrease in neonatal death, chronic lung disease or cerebral abnormality ($p=0.02$). However, in the co-amoxiclav groups, there was a significant increase of necrotizing enterocolitis (NEC) ($p=0.0007$). This study concluded that erythromycin for PPROM <37 weeks is beneficial for neonatal health and prolongation of pregnancy. However, co-amoxiclav cannot be recommended for PPROM because of the increased association with NEC.

Kenyon *et al* [34] did a meta-analysis in the Cochrane Review of 19 trials, including over 6000 women. ORACLE I and the NICHD study dominated the analysis. This meta-analysis supports routine use of antibiotics such as erythromycin in PPROM, and that co-amoxiclav should be avoided because of the increased risk of NEC.

WIDESPREAD ANTIBIOTIC USE

Antibiotic treatment is frequent and there is an ever-increasing pressure to give antibiotics to prevent preterm birth and reduce neonatal infection. However, antibiotics can alter cervical microflora and lead to the emergence of antibiotic-resistant infections in mothers and neonates.

Towers *et al* [35] demonstrated an increased incidence of early onset neonatal sepsis with non-GBS organisms resistant to ampicillin and recommends using Penicillin G for GBS prophylaxis (37), Mercer *et al* [36] analyzed outcomes for 8474 pregnancies at 6 hospitals and found ampicillin resistance in 45% of infants with sepsis.

It is not recommended to withhold antibiotics, but rather, to discourage use of antibiotics where a reduction in morbidity has not been demonstrated. It is important to administer agents with the narrowest possible effective antimicrobial spectrum.

SUMMARY OF RECOMMENDATIONS:

BACTERIAL VAGINOSIS

- If symptomatic, treat in any trimester.
- If asymptomatic, routine screening is not recommended.
- If there has been a previous preterm birth (high risk), screening is an option.
- If positive for BV and high risk, treat with oral metronidazole for one week. Vaginal treatment is not effective.

TRICHOMONAS VAGINALIS

- If symptomatic, treat in any trimester.
- If asymptomatic, routine screening is not recommended.

CHLAMYDIA AND GONORRHEA

- Screen and treat routinely, to prevent vertical transmission.

UREAPLASMA UREALYTICUM

- Routine screening is not recommended.

ASYMPTOMATIC BACTERIURIA

- Screen and treat routinely to decrease risk of pyelonephritis and preterm delivery.

GROUP B STREPTOCOCCUS (37)

- Bacteriuria: With presence of any organisms, treat when diagnosed.
- Do not treat positive vaginal cultures

antenatally.

- Routine screening for GBS at 35 – 37 weeks.
- Follow guidelines for intrapartum GBS prophylaxis.

PRETERM LABOUR, INTACT MEMBRANES

- No routine antibiotics to prevent preterm birth, but treat for GBS prophylaxis as per intrapartum GBS guidelines.

PRETERM PREMATURE RUPTURE OF MEMBRANES (PPROM)

- Follow GBS guidelines intrapartum.
- Ampicillin + Erythromycin for 7 days (Mercer *et al*) where benefits/risks are highest (24-32 weeks) to reduce neonatal morbidity and prolong pregnancy.
- Erythromycin alone may be used up to 37 weeks gestation. (ORACLE I).
- Do not use co-amoxiclav (increase in NEC).

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Neonatal Resuscitation Program (NRP): How we achieved 100 % participation

Judy Sloan, Reg. Nurse, NRP Instructor
South Bruce-Grey Health Centre (Walkerton)

WITH ALL THE DEMANDS ON physicians with office commitments, on-call duty and hospital rounds, how do you get physicians to take yet another course?? Most of the physicians at South Bruce-Grey Health Centre - Walkerton had taken NRP several years ago when it was offered through the Perinatal Outreach Program. Since then it has been difficult to get their neonatal resuscitation training renewed. At the Walkerton hospital, 100% of the obstetric nursing staff have been trained in NRP since it began. When the midwives joined the hospital maternal/child team, NRP registration was also required for them to practise.

Over the years, neonatal resuscitation training had been offered for staff on Wednesdays and Saturdays evenings at no cost, but this garnered very little participation. With an accreditation survey in 2002, however, the hospital received a key recommendation given high priority ... "to promote physician training in neonatal resuscitation!"



The Perinatal Outreach team in London was contacted for suggestions:

1. Offer Mainpro credits for physician training.
2. One of the Perinatal Outreach neonatologists could assist with teaching physicians.
3. Present the need for NRP to the medical staff meeting as a recommendation of high priority.

WHAT WORKED:

1. Each Physician was sent a letter informing them of the recommendation from the accreditors stating:

"Since GP's who deliver are limited in

number, and access to specialists is available only by referral out of town, neonatal resuscitation training is viewed as an urgent item to address. Without NRP we will have reduced capacity to respond to neonatal emergencies."

Staff were also informed that the hospital would be required to report changes that had been implemented, based on recommendations, to the survey team within six months.

2. An offer was made to teach physicians in whatever manner was most suitable to them, either one-to-one, in pairs or in groups.
3. Personal contact was made to follow-up with any physician that had not signed up for NRP instruction so that individual arrangements could be made.
4. All physicians were given the option to write the test before the hands on practical session.
5. Refreshments were provided!!

RESULTS:

Of nine physicians who offer obstetrical services in Walkerton, 100% have received instruction in NRP. Seventy-eight percent of physicians (7 of 9) are still currently registered in NRP. All of the nurses involved in maternal/newborn care and all midwives have received neonatal resuscitation training. NRP renewal is due this fall and in the spring of 2005. We anticipate 100% NRP registration once again.

FOR YOUR INFORMATION:

CONGRATULATIONS!!

... | s extended to South Bruce-Grey Health Centre – Walkerton. Having recently conducted a Hospital Perinatal Review in Walkerton Hospital, the Perinatal Outreach Team was very pleased to note that the hospital has achieved neonatal resuscitation training and registration for 100% of the physicians, midwives, and nurses providing maternal/newborn care. Thanks go to Judy Sloan, RN, NRP Instructor, for her dedication and hard work. (See Judy's article on page 6).



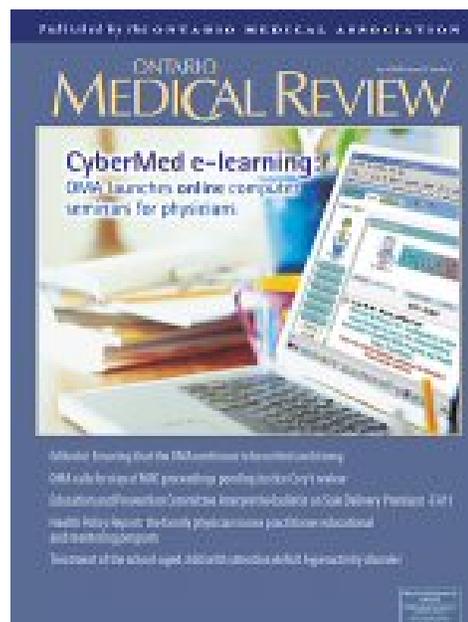
... | s extended to the Southwestern Ontario Perinatal Partnership (SWOPP) for their journal article entitled "WHO Principles of Perinatal Care Self-Evaluation Tool: Southwestern Ontario Results", which was published in the Ontario Medical Review, April 2004. The article highlights the development of a hospital self-evaluation tool based on "The Ten World Health Organization (WHO) Principles of Perinatal Care":

1. CARE FOR NORMAL PREGNANCY AND BIRTH SHOULD BE DEMEDICALIZED
2. CARE SHOULD BE BASED ON THE USE OF APPROPRIATE TECHNOLOGY
3. CARE SHOULD BE EVIDENCE-BASED
4. CARE SHOULD BE REGIONALIZED
5. CARE SHOULD BE MULTIDISCIPLINARY

6. CARE SHOULD BE HOLISTIC
7. CARE SHOULD BE FAMILY-CENTRED
8. CARE SHOULD BE CULTURALLY APPROPRIATE
9. CARE SHOULD INVOLVE WOMEN IN DECISION-MAKING
10. CARE SHOULD RESPECT THE PRIVACY, DIGNITY, AND CONFIDENTIALITY OF WOMEN

Measurable indicators were developed based on each of the principles and formatted into a survey that hospitals in the region were able to use for self evaluation and for comparison with units of similar birth volume. With 100% participation of hospitals in the region, this has been a useful way for hospitals to identify their successes and areas which could use improvement.

The article can be viewed in its entirety in the April 2004 issue of the *Ontario Medical Review* available on their website at <http://www.oma.org/pcomm/omr/apr/04maintoc.htm> Click on article # 32.



For further information, contact Nancy Dodman at:
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 (519) 646-6100 x 65900

UPCOMING EVENTS:

Mark Your Calendar!

ALARM COURSE

Midland: October 15-16, 2004
 Toronto: November 28-29, 2004
 (in conjunction with ON CME)
 For more information, contact the SOGC
 1-800-561-2416 / www.sogc.org
 Or contact Linda Kollesh CME/ALARM Program
 office at: lkollesh@sogc.com
 (613) 730-4192 or (800) 561-2416 x 247

MATERNAL NEWBORN NURSE EDUCATION COURSE

London:

Mondays: Sept 13 – Nov. 8, 2004*
 St. Joseph's Health Care, London
 (*excluding October 11, 2004)

Contact:

Gwen Peterek
 Perinatal Outreach Program
 Phone: (519) 646-6100 ext 65901
 Fax: (519) 646-6172
Gwen.peterek@sjhc.london.on.ca

Simcoe:

Thursdays: Sept. 9 – Oct. 21, 2004
 Norfolk General Hospital, Simcoe

Contact: Dodie Trimble (519) 426-0750

Chatham:

Fridays: Sept. 10 - Oct. 22, 2004/08/03
 Chatham Kent Health Care

Contact: Brenda Foster (519) 437-6021

SOUTHWESTERN ONTARIO PERINATAL PARTNERSHIP

Wednesday, October 20, 2004
 Location: Lamplighter Inn, London

Contact: Perinatal Outreach Office
 (519) 646-6100, ext. 65859

FETAL HEALTH SURVEILLANCE WORKSHOP

October 6, 2004
 Location: Hanover & District Memorial Hosp,
 Hanover

Contact: Vivian Niesen
 (519) 364-2340 x 239

BREASTFEEDING: WHEN EXTRA CARE IS NEEDED, EFFECTIVE STRATEGIES FOR THRUSH, MILK SUPPLY & WT GAIN ISSUES

November 15, 2004
 Location: Four Points Sheraton, London
 Visit the La Leche League website for more
 information
WWW.LLLC.CA/EVENTS/HPS_HOOVER/INDEX.PHP

19TH ANNUAL REGIONAL PERINATAL OUTREACH CONFERENCE

"EDUCATE, SHIFT, EVOLVE: THE FUTURE IS NOW"

Wednesday, Sept. 29, 2004

Location: Lamplighter Inn, London

Contact: Perinatal Outreach Office
 (519) 646-6100, ext. 65859

Registration forms can also be printed from our webpage:

www.sjhc.london.on.ca/sjh/profess/periout/periout.htm

REGIONAL NURSE MANAGER'S MEETING (for entire region)

Friday, Nov. 19, 2004

Location: Woodstock General Hospital

Contact: Perinatal Outreach Office
 (519) 646-6100, ext. 65859

NEONATAL-PAEDIATRIC TRANSPORT CONFERENCE – SOUTHWESTERN & NORTHERN ONTARIO REGIONS

Thursday, May 26, 2005

Location: London, Ontario

Contact:

Kris Kristjanson, Transport Coordinator
 PCCU & Paediatric Critical Care & Transport, LHSC
 (519) 685-8500 x 57380
kris.kristjanson@lhsc.on.ca

"BACK TO BASICS": LEVEL II NURSERY COURSE

Friday, October 29, 2004

Location: St. Joseph's Health Care, London
 Also available by videoconference to regional hospitals

Contact: Perinatal Outreach Office
 (519) 646-6100, ext. 65859

ACUTE CARE OF THE AT RISK NEWBORN (ACORN)

National Launch Nov. 15-16, 2004

Location: Lamplighter Inn, London

Details to be announced soon.

Contact: Perinatal Outreach Office
 (519) 646-6100, ext. 65859



This newsletter is a publication of the Perinatal Outreach Program of Southwestern Ontario.

Letters, queries and comments may be addressed to:

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To have your name included on our mailing list, please contact the above, or
 E-mail: gwen.peterek@sjhc.london.on.ca
www.sjhc.london.on.ca/sjh/profess/periout/periout.htm