Perinatal Outreach Program of Southwestern Ontario

Partner

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MRC Preterm Labour Study

Role of Endocrine and Infectious Markers in Predicting Preterm Birth in Symptomatic Women

As a Community Physician/Midwife, how can I help?

Preterm birth continues to be one of the major challenges in provision of perinatal care in Southwestern Ontario as well as world wide. The incidence of preterm birth has been estimated to be approximately 7% for North America and in Ontario it occurs in 6.3% of all births. Despite representing the minority of births, preterm birth contributes overall to approximately 75% of all neonatal mortality and morbidity with associated emotional, social, and financial costs. Although antenatal administration of glucocorticoids has been shown to improve the neonatal outcome for preterm infants, as has perinatal regionalization and advances in neonatal intensive care, our ability to accurately diagnose women in true preterm labour remains less than satisfactory. An improved ability to diagnose true preterm labour would be helpful in identifying women requiring ongoing hospitalization in a Level 3 Unit as well as more judicious use of glucocorticoids and potent tocolytic agents.

The Medical Research Council of Canada has recently funded a research project that aims to:

1) to determine the clinical utility of combined measurements of biochemical markers of fetal and maternal stress as well as subclinical infection in predicting subsequent preterm birth in women with threatened preterm labour;
2) to determine the prevalence of bacterial vaginosis and abnormal vaginal microflora in women with threatened preterm labour and correlate this with subsequent preterm birth; and
3) to examine the molecular mechanisms for the endocrine and paracrine hormones known to be important in the onset of parturition within the placenta and membranes of women who give birth and relate these to maternal biochemical markers obtained prospectively.

Previous work by the University of Western Ontario and St. Joseph's Health Centre team has shown that levels of corticotrophin-releasing-hormone (CRH) which is a small peptide produced by the placenta and present in the maternal circulation are 2-3 fold greater in women presenting with threatened preterm labour who actually go on and give birth within 24 hours when compared to those who do not (1). Another endocrine variable which has been suggested to be predictive of preterm birth is salivary estriol (2) which is an indirect marker of fetal "stress". A number of studies have reported an increased prevalence of preterm labour in women with bacterial vaginosis (3) and this study will therefore determine the incidence of bacterial vaginosis in women with threatened preterm labour as well as the nature of the vaginal microflora including lactobaccilli. The presence of fetal fibronectin (an extracellular matrix protein) in cervical vaginal secretions has been also reported to be an accurate predictor of true preterm labour and has been incorporated clinically in some centres in the United States (4). This study will examine the clinical utility of this protein as a marker of impending preterm birth. In women who go on to give birth prematurely, the placenta and membranes will be studied carefully for the gene expression of the key enzymes known to be important in the pathogenesis of preterm labour.

What's Inside...

This study is being conducted by a team of investigators including Dr. A. Bocking, Dr. K. Campbell, Dr. G. Reid, and Dr. J.R.G. Challis. It is anticipated that enrollment for this study will continue for 18-24 months. All women who present to the Labour and Birth area at St. Joseph's Health Centre who meet the inclusion criteria for the study will be approached and invited to participate in this study.

The inclusion criteria are:

1) 22-36 weeks gestation
2) singleton pregnancy
3) signs and symptoms of preterm labour (uterine contractions, increased pelvic pressure, vaginal discharge or low back pain).

The exclusion criteria are:

1) history or physical findings of ruptured membranes
2) presence of active bleeding (abruptio placenta, placenta previa)
3) major fetal abnormalities
4) intrauterine growth restriction (> 2 SD below mean for estimated fetal weight)
5) betamethasone administration within 7 days
6) pre-gestational diabetes
7) polyhydramnios (amniotic fluid pocket greater than 8 cm.)
8) preeclampsia
9) clinical evidence of chorioamnionitis / urinary tract infection
10) cervical dilatation > 4 cm..

It is recognized that on occasion, women in threatened preterm labour are administered betamethasone prior to transfer to St. Joseph's Health Centre. Because glucocorticoids increase the levels of CRH in the maternal circulation, we will be requesting where possible, that betamethasone administration be withheld until the patient arrives at S. Joseph's Health Centre. This, however, should be discussed with the receiving Obstetrician prior to transfer of the patient. We thank you for your support of this Research project and periodic updates will be provided in subsequent Newsletters.

For further information or answers to any questions regarding this study, please contact either Lorna Froste, RN, Study Coordinator, at 646-6000 Pager 0655, or Dr. Alan Bocking at 646-6106.

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Management of the Third Stage in Births With No Apparent Risk Factors

Although it is generally an anti-climatic event for the mother of a newly born baby, the third stage of labour is sometimes anxiety-provoking for the care provider, who is (or should be) aware of the potential hazards associated with it. Most often, the third stage is completed with the easy expulsion of the placenta and minimal maternal blood loss. However, ensuring that third stage is managed effectively requires a sound understanding of the physiology and principles for safe delivery of the placenta on the part of those providing care to labouring women.

Physiology of Third Stage

The third stage of labour consists of two phases; placental separation and placental expulsion. Both are effected by uterine contractions, which resume after a brief pause following the birth of the baby, and occur every 4 to 5 minutes thereafter. Separation occurs as a result of the sudden decrease in the size of the uterine cavity during and after the birth, as the uterus continues to contract down on the reduced contents within. As the uterus contracts, the site of placental attachment decreases in size, while the size of the placenta, of course, remains unchanged. The stress thereby created causes the placenta to buckle, and it is sheared from the uterine wall[1]

Separation most often begins in the central portion of the placenta, resulting in the formation of a haematoma between the placenta and remaining decidua. The retroplacental clot is thought to facilitate the completion of separation, as the additional weight in the mid-point of the placenta

helps to strip the adherent lateral borders, and to peel the membranes from the uterine wall[2].

Once it has separated, the placenta descends into the lower uterine segment or into the upper vaginal vault, which may cause any of the following clinical signs of separation to become evident:

1. Sudden trickle or small gush of blood
2. Lengthening of the amount of umbilical cord visible at the introitus
3. Change in the size of the uterus from discoid to globular, as the uterus now contracts on itself
4. Change in the position of the fundus, which rises to or above the umbilicus, as the bulk of the placenta in the lower segment or vaginal vault displaces it upward[1].

The expulsion of the placenta from the uterus occurs by one of two mechanisms. The more common Schultz mechanism results with the fetal side of the placenta presenting at the introitus, with the membranes inverted, trailing behind the placenta, and containing the retroplacental clot. The less common Duncan mechanism causes the placenta to escape sideways, like a button through a buttonhole, with the maternal side presenting first. The membranes in this presentation are not peeled off as effectively, and may more often be delayed or retained[3]. It is thought that the two mechanisms occur as a result of the original site of attachment in the uterus,with higher implantations resulting in a Schultz presentation while placentae attached lower in the uterus slide out by the Duncan mechanism[4]. Once expulsion of the placenta has occurred, bleeding from the placental site is controlled by the contraction of the "living ligature" of the oblique uterine muscle fibres in the upper uterine segment about the uterine blood vessels. As well, coagulation and fibrinolytic systems are activated, securing hemostasis by the formation of a fibrin "mesh" over the placental site[2].

There is some debate regarding the duration of a normal third stage. One retrospective review of 12,979 singleton vaginal births in which prophylactic oxytocic preparations were rarely administered demonstrated that the length of third stage ranged, in the majority of cases, between 4 and 10 minutes. After 30 minutes duration, there was an increase in postpartum haemorrhage (PPH) regardless of whether the placenta delivered spontaneously, or was manually removed[5].

Management of Third Stage

Ideally, the management of third stage in low-risk births begins in the antenatal and intrapartum periods, with the identification of factors which may predispose to complications in the third stage. A history of previous PPH or retained placenta, a prolonged first or second stage of labour, precipitous labour, birth of a macrosomic infant, or augmentation or induction of labour with oxytocin should lead the practitioner to employ active management techniques in third stage[6]. (There are, of course, additional factors to be considered in caring for the woman with a pregnancy at risk.) The practitioner would also do well to remember that, contrary to popular perception, the nulliparous woman is at higher risk for PPH, far more so than the grand multipara[7], and that two-thirds of PPH occur without predisposing factors[6].

Just exactly how third stage should be managed, however, is somewhat controversial. Obstetrical texts, for example, contradict each other. For example, while British and Australian texts are proponents of controlled cord traction, a popular American text, *Williams Obstetrics*, strongly admonishes its readers, in bolded text, never to employ the technique[8]. There has also been considerable discussion regarding the use of uterotonic preparations in more actively managing the third stage of labour.

Four randomized controlled trials have been conducted in Great Britain and Ireland to date, investigating active and physiologic methods of managing third stage[9,10,11,12]. Three of these appear to clearly indicate that active management (described as consisting of an oxytocic administered with the anterior shoulder, early cord clamping and controlled cord traction) confers distinct advantages to the mother with respect to reduced PPH and its sequelae. However, these studies need to be considered more closely before applying their results to practice.

First, the oxytocic drugs employed in the active management regimen in these trials were either Syntometrine (a combination of 5 IU oxytocin and 0.5 mg Ergometrine) or 0.5 mg Ergometrine (ergonovine maleate). The combination of ergot alkaloids and oxytocin have been demonstrated in meta-analysis to reduce PPH more effectively than oxytocin alone[13]; it is possible, therefore, that using only oxytocin in these trials would have resulted in somewhat different outcomes. (Interestingly, the

one trial where active management was demonstrated not to be beneficial was the one in which Ergometrine alone was used in active management[11].) Ergometrine has fallen into disfavour in North America, no doubt because of the maternal side effects of hypertension, nausea and vomiting associated with its use. However, it would seem erroneous to assume (although the authors of the Hinchingbrooke trial do) that oxytocin and Syntometrine are interchangeable in terms of reducing postpartum bleeding.

The term "physiologic management" in these trials does not refer just to avoiding the use of oxytocic drugs, as one might assume. Rather, it describes a regimen which includes no routine use of oxytocics, no clamping of the umbilical cord until pulsations cease, no uterine manipulation or controlled cord traction, and delivery of the placenta by maternal effort within 1 hour of birth. Full physiologic management, as defined here, is not commonly used by practitioners in North America. However, care providers who do not routinely administer oxytocin, but who do, for example, employ controlled cord traction (sometimes called the Brandt-Andrews manoeuvre), may consider their management style to be physiologic rather than active. Yet, in the context of these trials, such practices fall into neither category.

Controlled cord traction, however, is a component of active management that is somewhat overlooked as an effective step in third stage management. Two older trials have suggested that controlled cord traction is associated with lower mean blood loss and shorter third stages[14] than less active approaches (including use of fundal pressure). These findings have been borne out by a more recent RCT[15], although the results of this trial may be confounded somewhat by differences in the timing and route of administration of oxytocin between the study groups. Further investigation into the role of controlled cord traction in managing third stage would be useful.

Bearing in mind what has already been suggested in the literature about the association between prolonged third stage and complications, it may well be that the most important aspect of third stage management is minimizing its duration; how that is accomplished may be secondary. It is interesting to note that in two trials demonstrating active management to be the superior approach[10,12], 26% and 16.4% of women in the physiologic groups had third stages exceeding 30 minutes (compared to 2.9% and 3.3% of women in the active management groups). In the Dublin trial[11], however, which demonstrated no benefit to active management, third stage duration was less than 20 minutes in 93% of the physiologically managed and 95% of the actively managed groups respectively.

Given the incomplete evidence which currently exists, it would still seem prudent for those providing care to low-risk women during labour and birth to employ techniques to expedite the expulsion of the placenta. In cases where a woman has a clearly increased risk for excess blood loss, the prophylactic use of oxytocin should be included as part of management. Similarly, for women with epidural anaesthesia, oxytocin is easily administered intravenously as part of third stage management. However, when caring for women who give birth without pain medication and who have no increased risk for PPH, care providers should remember that intramuscular oxytocin is experienced by most women as being relatively painful, and be selective in its use.

When performing controlled cord traction to manage third stage, it is important to observe some key principles. Controlled cord traction should not be attempted prior to separation of the placenta, and should only be done in the presence of a well-contracted uterus, in order to avoid the potential danger of uterine inversion. While performing cord traction, the non-dominant hand of the practitioner should rest on the abdomen with the heel of the hand at the symphysis pubis, and the fingertips resting on the fundus. In this manner, s/he can confirm that the uterus is contracted and is also able to detect any "dipping" in the fundus, indicative that the placenta has, in fact, not separated (and that traction should be discontinued until it has), as well as "guarding" the uterus in the traditional manner.

During traction, the mother may be asked to push to assist expulsion. This may be of particular use in situations where the cord is beginning to avulse, and the practitioner wishes to use minimal traction in facilitating expulsion. As the placenta begins to appear at the introitus, the non-dominant hand continues to guard the uterus by applying pressure downward and slightly toward the umbilicus until the placenta is completely expelled.

In this manner, third stage may be managed with a minimum of discomfort for the new mother, while

reducing her risk of excess blood loss. Although childbearing women, of course, have individual preferences regarding the conduct of their labour and birth, which should be discussed with her care provider in advance of the event, most women regard a prolonged third stage as a negative experience[16]. With careful management, third stage can remain an anti-climatic and uneventful part of one of the most important days of a woman's life.

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I am indebted to Dr. Renato Natale for teaching me this particular refinement of uterine guarding.

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You Asked Us...

Answers To Frequently Asked Questions On Maternal Serum Screen (MSS)

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Jack Jung, MD, FRCP(C), FCCMG, Regional Medical Genetics Centre, Chidren's Hospital of Western Ontario, London
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Jo-Ann Kane, RN, Bsc Genetic Coordinator, Regional Medical Genetics Centre, Children's Hospital of Western Ontario, London

1. When should the sample be collected?

Although the laboratory will provide an interpretative report on samples taken between 15 weeks and 0 days to 20 weeks and 6 days, the recommended time is at 16.0 weeks. A report will be generated within 5 working days after specimen collection. All high risk reports will be phoned to the physician's office. To allow time for follow-up procedures (confirmation of gestational age, genetic counselling), it is highly recommended that specimen collection not be delayed to the later gestational ages (ie: > 16 weeks).

2. How is the gestational age assigned?

If ultrasound data is provided, the gestational age will be derived using BPD measurements from the table shown on page 7. Early ultrasounds (less than 10 weeks and 6 days), CRL measurement will be used). The gestational age derived is then extrapolated to the specimen collection date. If no ultrasound is provided, LMP (yy/mm/dd) is used. If LMP only is provided, the patient should be very certain and cycles should be regular and 28 days.

3. When will a report be amended?

When an ultrasound shows 10 days or a larger gestational age gap from that calculated by LMP. A report will also be amended if any information on the report is incorrect (usually this is due to a clerical error on the requisition). The experience so far is that 29% of the screen positives for Down Syndromes based on LMP dating are off by 10 or more days when checked with ultrasound and are

then determined to have been done too early and an amended report is issued.

4. **When should a repeat specimen be taken?**
A repeat specimen will be requested when the sample is taken too early, or AFP is slightly elevated (2.00-3.00 MoM), provided there is time for repeat collection (patient is less than 19.0 weeks of gestational age). Repeat specimen is not recommended for the confirmation of screen positive for Down or Trisomy 18.

5. **What is the cutoff risk for Trisomy 18?**
A report will be interpreted as high risk for Trisomy 18 if the risk is higher than 1:100.

6. **What if the patient has a family history of Down or Trisomy 18 or Neural Tube Defects?**
Presently, the higher prevalence in these populations are not taken into consideration in calculating risks. The report should be interpreted with caution, and risks discussed with geneticists.

7. **How is the patient informed of the test?**
Patient brochures are available in several languages from the Regional Genetics Centre, Tel: (519) 685-8140. It is important that the patient understands the Pros and Cons of the test before the test is performed.

8. **What are the Pros and Cons of the test?**
MSS is not a diagnostic test but rather a screening test. It provides the chances of an adverse outcome and as such can cause anxiety to the patient. The advantage of the test, however, is that it allows screening on an individual basis for pregnant women of all ages and, therefore, risk assessment for the chance of chromosomal abnormalities in women less than age 35, who want to know such information. It is known that 70% of Down babies are born to women who are less than 35 years of age and, therefore, would not have been offered amniocentesis.

9. **What are the Sensitivities and the Specificities of the MSS test?**
The detection rates are:

70% for Down Syndrome in general (detection rate is lower in women less than 35 years and higher in women more than 35 years of age)

77% for Open Spina Bifida

False positive rates of:

8% for Down Syndrome
1.7% for Open Spina Bifida
0.2% for Trisomy 18

The Provincial Data Base shows that when amniocentesis is offered based on age alone, the number of amnios per detected Down Syndrome is 200. If amniocentesis is offered based on positive MSS screen, the number of amnios per detected Down Syndrome is 70 (ie: MSS is much more efficient as a screen for Down Syndrome as compared to maternal age alone).

10. **What does a Screen Negative test mean?**
Most of the time the fetus is not affected. However, a screen negative is not 0% risk and a small number of fetuses can have adverse effects. It is important that the ordering physician verifies the accuracy of dating (with less than 10 day difference from LMP) to minimize chances of missed high risk fetuses.

11. **How can I reach the Regional Genetics Centre?**
Genetics Telephone Number: (519) 685-8140
Laboratory Telephone Number: (519) 667-6592

➲ *Please see the table on page 7*

For Your Information...

"ESSENTIAL MANAGEMENT OF OBSTETRIC EMERGENCIES"
By Thomas F. Baskett
Dalhousie University, Halifax, Nova Scotia
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GESTATIONAL AGE (WEEKS & W+D) FROM CROWN RUMP LENGTH AND BIPARIETAL DIAMETER FOR USE WITH MATERNAL SERUM SCREENING. US Subcommittee. July 1998.

CRL age		mm	BPD age	
6.1	(6+1)	2		
6.3	(6+2)	3		
6.4	(6+3)	4		
6.6	(6+4)	5		
6.7	(6+5)	6		
6.9	(6+9)	7		
7.0	(7+0)	8		
7.2	(7+1)	9		
7.3	(7+2)	10		
7.4	(7+3)	11		
7.6	(7+4)	12		
7.7	(7+5)	13		
7.9	(7+6)	14		
8.0	(8+0)	15	(10+6)	10.9
8.1	(8+1)	16	(11+1)	11.1
8.3	(8+2)	17	(11+3)	11.4
8.4	(8+3)	18	(11+5)	11.7
8.5	(8+4)	19	(12+0)	12.0
8.7	(8+5)	20	(12+2)	12.2
8.8	(8+6)	21	(12+4)	12.5
8.9	(8+6)	22	(12+5)	12.8
9.0	(9+0)	23	(13+0)	13.1
9.2	(9+1)	24	(13+2)	13.3
9.3	(9+2)	25	(13+4)	13.6
9.4	(9+3)	26	(13+6)	13.9
9.5	(9+4)	27	(14+1)	14.2
9.6	(9+4)	28	(14+3)	14.5
9.7	(9+5)	29	(14+5)	14.7
9.9	(9+6)	30	(15+0)	15.0
10.0	(10+0)	31	(15+2)	15.3
10.1	(10+1)	32	(15+4)	15.6
10.2	(10+1)	33	(15+6)	15.9
10.3	(10+2)	34	(16+1)	16.2
10.4	(10+3)	35	(16+3)	16.5
10.5	(10+3)	36	(16+6)	16.8
10.6	(10+4)	37	(17+1)	17.1
10.7	(10+5)	38	(17+3)	17.4
10.8	(10+6)	39	(17+5)	17.7
10.9	(10+6)	40	(18+0)	18.0
11.0	(11+0)	41	(18+2)	18.3
11.1	(11+0)	42	(18+4)	18.6
11.2	(11+1)	43	(18+6)	18.9
11.2	(11+2)	44	(19+2)	19.2
11.3	(11+2)	45	(19+4)	19.5
11.4	(11+3)	46	(19+6)	19.9
11.5	(11+4)	47	(20+1)	20.2
11.6	(11+4)	48	(20+4)	20.5
11.7	(11+5)	49	(20+6)	20.8
11.7	(11+5)	50	(21+1)	21.2
11.8	(11+6)	51	(21+3)	21.5
11.9	(11+6)	52	(21+6)	21.8
12.0	(12+0)	53	(22+1)	22.2
12.0	(12+0)	54	(22+4)	22.5
12.1	(12+1)	55	(22+6)	22.8
12.2	(12+1)	56	(23+1)	23.2
12.2	(12+2)	57	(23+4)	23.5
12.3	(12+2)	58	(23+6)	23.9
12.4	(12+3)	59	(24+2)	24.2
12.4	(12+3)	60	(24+4)	24.6
12.5	(12+3)	61	(25+0)	25.0
12.6	(12+4)	62	(25+2)	25.3
12.6	(12+4)	63	(25+5)	25.7
12.7	(12+5)	64	(26+0)	26.1
12.7	(12+5)	65	(26+3)	26.4
12.8	(12+5)	66	(26+6)	26.8
12.8	(12+6)	67	(27+1)	27.2
12.9	(12+6)	68	(27+4)	27.6
12.9	(12+6)	69	(28+0)	28.0
13.0	(13+0)	70	(28+2)	28.3
13.0	(13+0)	71	(28+5)	28.7
13.1	(13+0)	72	(29+1)	29.1
13.1	(13+1)	73	(29+4)	29.5
13.1	(13+1)	74	(30+0)	29.9
13.2	(13+1)	75	(30+2)	30.4
13.2	(13+1)	76	(30+5)	30.8
13.2	(13+2)	77	(31+1)	31.2
13.3	(13+2)	78	(31+4)	31.6
13.3	(13+2)	79	(32+0)	32.0
13.3	(13+2)	80	(32+3)	32.5
13.4	(13+3)	81	(32+6)	32.9
13.4	(13+3)	82	(33+2)	33.3
13.4	(13+3)	83	(33+5)	33.8
13.4	(13+3)	84	(34+2)	34.2
		85	(34+5)	34.7
		86	(35+1)	35.1
		87	(35+4)	35.6
		88	(36+0)	36.1
		89	(36+4)	36.5
		90	(37+0)	37.0
		91	(37+3)	37.5
		92	(38+0)	38.0
		93	(38+3)	38.5
		94	(39+0)	38.9
		95	(39+3)	39.4
		96	(40+0)	39.9
		97	(40+3)	40.5
		98	(41+0)	41.0
		99	(42+0)	41.5
		100	(42+4)	42.0

Hadlock. J Ultrasound Med 1:97, 1982. BPDage = 6.8954 + 0.26345*B + 0.000008771*B^3

Daya S. Am J O&G. 168:903, 1993. CRLage = (40.447 + 1.125*C - 0.0058*C^2)/7.

Dr. A. Toi, (416) 340-4800 ext. 8298#

Submissions Requested:

Does your hospital, health unit, or community have a successful project or programme, concerning perinatal health that you would like to share with your colleagues in Southwestern Ontario? We would love to hear from you!

Submissions should include a brief synopsis of your program (1,000 words or less), including a discussion of the method, evaluation, and a contact name. The Perinatal Outreach Program reserves the right to edit all submissions.

Upcoming Events:

ALARM *(Advances in Labour and Risk Management)*

An intensive two day course for physicians, nurses, and midwives, including the most recent clinical guidelines on high risk conditions during labour and birth. This course includes "hands on" workshops, group discussions, and a practical exam. This Canadian course was developed by, and is jointly taught by family physicians and obstetricians. It is offered by the Society of Obstetricians and Gynaecologists of Canada (SOGC) throughout 1999/2000 at various times across Canada. The proposed schedule for courses in Ontario for the Fall are:

Thunder Bay	October 22-23, 1999
Toronto	November 20-21, 1999
Toronto	December 4-5, 1999

For further information, please contact:

SOGC
774 Promenade Echo Drive
Ottawa, ON K1S 5N8

Tel: (613) 730-4192
1-800-561-2416

Fax: (613) 730-4314

Perinatal Outreach Program of Southwestern Ontario, 13th Annual Perinatal Meeting

"Benchmarking: Promoting & Assessing Quality in Maternal/Newborn Care"

Friday, September 24th, 1999
Best Western Lamplighter Inn London, Ontario

For more information, contact:
Gwen Peterek. Perinatal Outreach Program
Tel: (519) 646-6100, x 65901

Obstetrical Nursing Education Program

Hosted by the Perinatal Outreach Program of Southwestern Ontario will be offered in three locations this fall.

- St. Joseph's Health Centre, London
  Mondays: September 13 - November 1, 1999
  Contact: Susan Maleckie,
  (519) 646-6100, ext. 64365
- Chatham Kent Health Alliance
  Public General Campus
  Mondays: September 13 - November 1, 1999
  Contact: Brenda Foster,
  (519) 352-6400, ext. 2534
- Hanover District Hospital
  Thursdays: September 9 - October 21, 1999
  Contact: Alan Penfold, (519) 364-2340

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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