

Perinatal Challenges

As advancements are made in healthcare and technology, Canadians can take heart in knowing that there are many treatments, diagnostics and therapeutics now available that make conditions and diseases that would have been deadly just a few short years ago, now, relatively minor and treatable. However, as advancements are made there are new challenges to address as the cycle continues. Such is the case with pregnancy and fetal/maternal health.

In the last twenty years, we have seen a decrease of over 25% in the infant mortality rate in Canada. Furthermore, we have seen an over 38% decrease in the rate of infant deaths due to congenital malformations, testament to the advances over the last twenty years in prenatal diagnosis, termination of affected pregnancies and improvements in care of infants with congenital anomalies.

Where we have made these improvements, we add new challenges that must be addressed in the coming years. Canada is now experiencing an increase in the number of preterm deliveries, multiple births and an aging population of mothers. Many of these can be attributed to a change in our behaviours, couples are getting married later, women are establishing their careers before becoming mothers and having their children later in life during the time when their fertility is on the downtrend, resulting in more IVF procedures resulting in a higher incidence of multiple births, not only from the IVF treatments but also the increased incidence of multiple births in older women.

Preterm birth rates have increased from just over 6% in 1981 to almost 8% in 2002 and preterm birth rates among multiple live births is far more staggering, from 40% in 1981 to 53.5% in 2000. The Canadian Perinatal Health Report: 2000 states, "Preterm birth remains the most important perinatal challenge facing industrialized countries." The associated healthcare costs surrounding preterm births related to longer hospitalization, which may include neonatal intensive care, increased interventions as well as long term health care costs are estimated at \$676,800 (1995) per low birth weight baby.¹

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BIRTH

Biochemical screening for preterm labour is an important new area of research and investigation to find the diagnostic markers that will be able to aid physicians in determining the risk of preterm labour, as soon as possible and therefore take the appropriate indications to defer the onset of labour for as long as possible. Phosphorylated IGFBP-1 (pIGFBP-1) has been in use in Europe and Asia for many years and there are many studies showing its effectiveness, not only in determining the risk of preterm labour but also in determining the cervical ripeness for labour induction. According to several studies, the level of pIGFBP-1 rises considerably as the cervix matures, therefore making this marker an excellent tool to determine true term or preterm labour.



The cutoff is set so that a result under 10ug/L can effectively rule out delivery within the next two weeks. Conversely, a result over the cutoff indicates a high probability of preterm delivery, and therefore proper treatments can be indicated.

This marker is now available in Canada, distributed by Somagen™ Diagnostics. The test is a dipstick that is a fast and simple bedside test to measure the ripeness of the cervix during pregnancy, the actim™ Partus test, manufactured by Medix Biochemica, offers ease of use and is economical to use as many times as needed to monitor pregnancy. Please call for more information.

1 Preterm Birth Clinical Practice Guidelines: Best Start 2002 – Society of Obstetricians and Gynecologists of Canada

Increased Effectiveness in Cancer Screening

Colorectal cancer is the third most common form of cancer in Canada and the fourth leading cause of cancer mortality in the world. With this and the risks increasing in our aging population, early detection with effective screening is crucial.

A screening test should identify patients that require legitimate further investigation however there are several potential harms that must be considered against any potential benefit of screening for cancer. Some cancer screening tests can involve risks of serious complications that may be immediate (e.g., perforation with colonoscopy) or delayed (e.g., carcinogenesis due to a non sensitive method). Another harm is the false-positive test result, which may lead to anxiety and further unnecessary diagnostic procedures. Finally, a false-negative screening test may falsely reassure an individual with early clinical signs or symptoms of cancer and thereby actually delay diagnosis.

Currently the most commonly used screen for colorectal cancer looks for the presence of fecal occult blood that may be associated with a tumor. The most widely used screening kits utilize guaiac based tests to detect the presence of hemoglobin - limiting in that they detect the peroxidase activity associated with all forms of hemoglobin whether human or animal in origin, as well as other vegetable and dietary supplements such as vitamin C. This method then relies heavily on patient compliance with diet restrictions or risks the potential of false- positive results.

New monoclonal technology can now specifically detect human blood in fecal samples reducing the likelihood of false positive tests and requires no restrictions to diet. Actim™ Fecal Blood utilizes this more specific and sensitive monoclonal technology to detect human hemoglobin in quantities as low as 25 –50 µg per gram of feces (compared to some guaiac test cards at 2 mg per ml of sample) in a rapid easy format which presents no risk to the patient confidently meeting the criteria for cancer screening. Additional benefits of reduction in the cost of unnecessary repeats and invasive procedures are only second to receiving a confidently reported negative result.



BNP Improves Diagnostic Accuracy in the Emergency Department

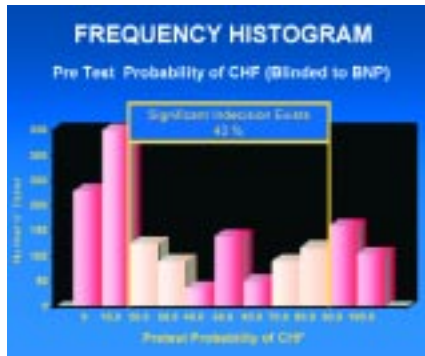


Figure 1

In a recent landmark study published in the New England Journal of Medicine, rapid availability of B-Type Natriuretic Peptide (BNP) significantly enhanced the diagnostic accuracy of Emergency Physicians in the evaluation of acute dyspnea (shortness of breath).⁽¹⁾

The Breathing Not Properly study was a seven-site, multinational study enrolling a broad population of 1586 participants who presented to the ED with a primary complaint of acute dyspnea. ED Physicians, blinded to the BNP results, were asked to estimate the clinical probability of CHF based on current evaluation criteria, including a physical exam, patient history, ECG, chest x-ray and other readily available diagnostic tests. As the graph indicates (Fig. 1) there is significant uncertainty amongst ED Physicians on whether they thought the patients' symptoms were from CHF or other causes of dyspnea.

Multivariate Analysis of Diagnostic Methods

Variable	Chi-Square	Significance	Odds Ratio
Hx CHF	464.6	<0.001	22.8
Capitalization c.	141.8	<0.001	16.8
Edema	91.2	<0.001	4.9
Rales	36.1	<0.001	2.0
Hx MI	22.6	<0.001	3.2
Age >75	16.0	<0.001	2.2
JVD	15.0	<0.001	2.6
Third heart sound	12.5	<0.001	4.9
Dyspnea	10.0	<0.001	1.8
Atrial fibrillation	11.3	<0.001	3.0
BNP <100 pg/mL	225.8	<0.001	28.9
If BNP analyzed first			
BNP 100	647.3	<0.001	42.4

Figure 2

Two Cardiologists, also blinded to the BNP results, reviewed all medical records pertaining to the patient during the initial ED visit and any subsequent follow up testing and independently classified the patients as having CHF or not. Retrospective analysis of the data indicated a point of care BNP result would have reduced clinical indecision by a whopping 74%. In addition, BNP was the single, most accurate predictor of the presence or absence of CHF, with an odds ratio of 28:90 (Fig. 2). The areas under the receiver operating characteristics curve indicate

that BNP provides added diagnostic value over and above the current evaluation tools. (Fig. 3) The areas under the receiver operating characteristic curve (AUC) were 0.86, 0.90 and 0.93 for clinical judgment, for BNP at a cutoff of 100 pg/mL, and for the two in combination, respectively. The calculated area under the curve of 0.90 was similar when compared to that of other heavily relied upon laboratory diagnostic aids. For example, close comparison to prostate specific antigen for the detection of prostate cancer (AUC = 0.94) and superior to those of Papanicolaou smears and mammography (AUC = 0.70 and 0.85 respectively).



Figure 3

The findings of this study indicate rapid BNP added significant, independent predictive power to other clinical variables in models predicting which patients had CHF. The value of natriuretic peptides has already been recognized by their inclusion in the recent Canadian and European guidelines for the diagnosis of chronic heart failure.^(2, 3)

Based on the study results and the current state of the Canadian health care system, we can hypothesize that a laboratory which implements point of care BNP testing has the ability to contribute to faster clinical decision, faster patient disposition and treatment as well as limiting overcrowding issues in the Emergency Department ultimately reducing costs.

For a copy of the Breathing Not Properly study or information on Triage BNP, please call Brian Roskewich, Point of Care Specialist at 1-800-661-9993 ext. 9532.

- 1) Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid Measurement of B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure. *N Engl J Med.* 2002;347:161-167.
- 2) Liu P, et al. The 2001 Canadian Cardiovascular Society Consensus Guideline Update for the Management and Prevention of Heart Failure. *Can J Cardiol* 2001;17 Suppl E:5E-24E.
- 3) Remme WJ, Swedberg K. Guidelines for the Diagnosis and Treatment of Chronic Heart Failure. *Eur Heart J* 2001;22:1527- 60.



Urine Protein Electrophoresis-Factors to consider when choosing a Concentrator

If you choose to concentrate urines for detection of Bence Jones Proteins on Urine Protein Electrophoresis (UPE) or Urine Immunofixation (UIF) there are some aspects of a concentrator that you may want to consider to optimize recovery of these proteins. The concentrator you choose becomes as important as the assay that is being used to detect the proteins.

Molecular Weight Cut Off

The Molecular Weight Cut Off (MWCO) is an important consideration for a concentrator. The Molecular Weight of Bence Jones proteins is typically around 20,000 – 24,000 Kilodaltons (kDa). Therefore, when choosing a concentrator, it is important to consider the MWCO of the membrane that is used in the concentrator. The MWCO quoted on any concentrator will have up to a 20% variation in the pores of the membrane. What does this mean? If you have a protein that you are trying to capture, you want to ensure that the pore size of the membrane is small enough that you are not losing valuable protein that you are indeed, trying to ultimately detect and measure. An optimum pore size for the capture of a Bence Jones protein will be around the 7,500 – 10,000 kDa mark (depending on type used) to ensure there is no loss of protein. If the concentrator has a pore size of 15,000 kDa, then the actual size of the pores within the membrane will vary between 12,000 to 18,000 kDa and this may be suspect.

Membrane Type

The type of membrane used in the manufacture of concentrators should be highly hydrophilic, when attempting to isolate proteins that are below 50,000 kDa molecular weight. This minimizes protein loss and ensures good recovery.

Static Versus Centrifugal

The pore size is an important consideration in a static concentrator but is even more important in consideration of a centrifugal concentrator. For example, the same pore size of 7,500 MWCO will have a remarkably different recovery in a static concentrator than in a centrifugal concentrator due to the force involved. The ideal pore size for the recovery of a Bence Jones protein in a centrifugal concentrator should be around 10,000 kDa.

Lastly, you may want to consider the ease of use of the product. Does the product enable you to use a plastic transfer pipet for added safety? Does the product have easy to read graduations for ease of reading?

Somagen now offers the Vivaproducts range of static and centrifugal concentrators for concentrating urines. The Vivaproducts address all of these concerns and have been manufactured for the precise application of recovery of Bence Jones Proteins. Call us for more details.



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