Instituting Surveillance Guidelines and Adverse Outcomes in Preeclampsia

*Jennifer Menzies, BSc, Laura A. Magee, MD, FRCPC, Jing Li, MSS, Ying C. MacNab, PhD, Ruihua Yin, MSc, Heather Stuart, BSc, Brandon Baraty, BSc, Elaine Lam, BSc, Trevor Hamilton, BSc, Shoo K. Lee, MBBS, PhD, and Peter von Dadelszen, MBChB, DPhil, for the Preeclampsia Integrated Estimate of RiSk (PIERS) Study Group**

OBJECTIVE: To assess the incidence of combined adverse maternal and perinatal outcomes in women with preeclampsia before and after introducing standardized assessment and surveillance.

METHODS: This study was a preintervention (retrospective) compared with a postintervention (prospective) cohort comparison in a single-tertiary, perinatal unit that included women admitted to hospital with preeclampsia. We interrogated an existing retrospective 24-month database and then introduced the guidelines, assessing the incidence of the combined adverse maternal and perinatal outcomes for 41 months (September 2003 through February 2007). Tests of organ (dys)function were performed at least as often as on the day of admission, admission day +1, every Monday and Thursday, day of delivery, and delivery day +1. All data were checked for errors. The combined maternal outcome was maternal death or one or more of hepatic failure, hematoma, or rupture, Glasgow coma score of less than 13, stroke, at least two seizures, cortical blindness, need for positive inotrope support, myocardial infarction, infusion of any third antihypertensive, renal dialysis, renal transplantation, at least 50% FIO_2 for greater than 1 hour, intubation, or transfusion of at least 10 units of blood products. The combined perinatal outcome was perinatal or infant mortality, bronchopulmonary dysplasia, necrotizing enterocolitis, grade III/IV intraventricular hemorrhage, cystic periventricular leukomalacia, or stage 3–5 retinopathy of prematurity.

RESULTS: Two hundred ninety-five and 405 women were in the preintervention and postintervention cohorts, respectively. The incidence of adverse maternal outcome fell (5.1% to 0.7%; Fisher $P<.001$; odds ratio 0.14, 95% confidence interval 0.04–0.49). Perinatal outcomes did not change.

CONCLUSION: Standardized surveillance of women with preeclampsia was associated with reduced maternal risk.

(Obstet Gynecol 2007;110:121–7)

LEVEL OF EVIDENCE: II

Preeclampsia remains a leading cause of maternal mortality in North America, and we have found that the surveillance of women with suspected or confirmed preeclampsia is variable between practitioners.[1] The mainstays of the management of severe preeclampsia include "full assessment of the mother and the baby, and delivery on the best day in the best way."[2]

It has been observed that standardizing care is associated with reduced adverse health outcomes across a range of disciplines and medical conditions.[3–14] Failure to standardize care has been associated with poorer outcomes.[14]

We have previously undertaken a multicenter retrospective study of 2 years of preeclampsia cases in

* *For members of the PIERS Study Group, see the Appendix.*

From the Departments of Obstetrics and Gynaecology, Health Care and Epidemiology, and Medicine, and the CFRI Centre for Healthcare Innovation and Improvement, University of British Columbia, Vancouver, British Columbia; Department of Ambulatory Care and Prevention, Harvard Medical School, Cambridge, Massachusetts; Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia; and Department of Paediatrics and iCARE, University of Alberta, Alberta, Canada.

Funded by grants from the Canadian Institutes for Health Research (operating grants to P.v.D. and S.K.L. and salary awards to P.v.D., S.K.L., and J.M. [STIRRHS award]), the Michael Smith Foundation for Health Research (operating grant to S.K.L. and salary awards to P.v.D. and L.A.M.), and the Child and Family Research Institute (salary award to P.v.D.).

The authors thank Pamela Lutley, Jonathan Lam, and Kelly Richardson for their research assistance.

Corresponding author: Dr. Peter von Dadelszen, University of British Columbia, Department of Obstetrics and Gynecology, 2H30-4500 Oak Street, Vancouver, BC V6H 3N1, Canada; e-mail: pvd@cw.bc.ca.

Financial Disclosure
The authors have no potential conflicts of interest to disclose.

ISSN: 0029-7844/07

three tertiary level units.[15] In that study, we tested a number of predictors of adverse maternal outcomes against a combined adverse maternal outcome derived by international Delphic consensus.[16,17] This combined adverse outcome reflects the systemic inflammatory nature of the maternal syndrome[18,19] and assesses all vulnerable organ systems.[19] In an era of generally adequate blood pressure control, maternal mortality associated with preeclampsia is largely due to the complications of systemic inflammation.[18]

Since the time of the retrospective study, we have developed guidelines for the assessment and ongoing evaluation of women admitted to our unit with a suspected or confirmed hypertensive disorder of pregnancy. Part of a continuous quality improvement initiative at British Columbia Women's Hospital and Health Centre (BC Women's), these guidelines were designed to evaluate comprehensively vulnerable organ function and to reflect both the variable presentation and the systemic nature of preeclampsia (gestational hypertension with either proteinuria or adverse conditions) and the other hypertensive disorders of pregnancy. They were derived from the pattern of investigation used in other centers of excellence, and in response to international guidelines,[20–22] to current practice across Canada[1] and preliminary evidence that it may be possible to identify those women most at risk of doing poorly.[15] In this paper we describe the incidence and pattern of adverse maternal and perinatal outcomes before and since introducing the guidelines.

MATERIALS AND METHODS

From the previous retrospective study,[15] we identified those patients who had been cared for at BC Women's, from January 2000 to December 2001. The criteria for inclusion in that study were admitted women with preeclampsia, the hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, or eclampsia. The same criteria were used for the prospective part of the study published here, although the guidelines cover all women with either hypertension in pregnancy or gestational proteinuria or both.

In this context, preeclampsia was defined as at least two of the following: 1) hypertension (systolic blood pressure of 140 mm Hg or greater and/or diastolic blood pressure of 90 mm Hg or greater, taken twice more than 4 hours apart) after 20 weeks of gestation, 2) proteinuria defined as 0.3 g/d or more or 2+ or more dipstick proteinuria after 20 weeks of gestation, 3) nonhypertensive and nonproteinuric HELLP syndrome, using Sibai's criteria,[23] or 4) an isolated eclamptic seizure without preceding hypertension or proteinuria, using the British Eclampsia Survey Team criteria to define eclampsia.[24]

These guidelines were developed as a minimum standard. The timing of the investigations was at least as frequently as the day of admission, admission day +1, every Monday/Thursday (ante- and postpartum), day of delivery, and delivery day +1. Additional clinical, laboratory, and ultrasound evaluations were performed whenever considered necessary or prudent by providers. There is no policy of mandatory subspecialty consultation.

In addition to routine measurement of maternal blood pressure, the investigations included the following:

1. Hematology: full blood screen, international normalized ratio (INR), activated partial thromboplastin time (APTT), and fibrinogen.
2. Renal: urea, creatinine, electrolytes, uric acid, and dipstick. While other testing occurred twice weekly, urine was also assessed by 24-hour urine for protein and creatinine clearance (on admission and once weekly thereafter [every Sunday/Monday]).
3. Hepatic: aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), bilirubin, albumin (plasma), and random glucose.
4. Respiratory: pulse oximetry.
5. Fetal surveillance (antenatally only): cardiotocography (CTG; daily), ultrasound for assessment of fetal weight (every 14 days), and amniotic fluid volume and umbilical artery Doppler (twice weekly).

These guidelines were introduced into practice in September 2003 through the North American practice of standing orders. Standing orders are preprinted forms used to standardize management to improve outcomes. The use of the standing orders was monitored each weekday by two of us (J.M. and B.B.), and those practitioners not using the orders were contacted to request their use. Using a pre-/postintervention study design, we examined the influence of introducing the guidelines on the incidence of the combined adverse maternal outcome.

The combined outcome was maternal death or one or more of hepatic failure, hematoma, or rupture, Glasgow coma score less than 13, stroke, two or more seizures, cortical blindness, need for positive inotrope support, myocardial infarction, infusion of any third antihypertensive, renal dialysis, renal transplantation, 50% or more FIO_2 for more than 1 hour, intubation, or transfusion of 10 or more units of blood products.[15] We also assessed a combined adverse perinatal outcome (Delphic consensus): perinatal or infant mortality, bronchopulmonary dysplasia, necrotizing enterocolitis, grade III or IV intraventricular hemorrhage,

cystic periventricular leukomalacia, or stage 3–5 retinopathy of prematurity.[15]

Specifically, comparisons were made based on the incidence among 295 women from the feasibility study of January 2000 to December 2001 (as preintervention) and 405 women with completed charts from the postintervention period of September 1, 2003, to February 28, 2007. Because the incidence was uncommon (particularly in the postintervention period), statistical analysis of rates and ratios were carried out by assessing Fisher exact test and odds ratio, using Prism 4.0 (GraphPad, San Diego, CA). For continuous variables (demographics), Student *t* test was used, unless otherwise stated. Significance was set at $P<.05$. The study was approved by the University of British Columbia Clinical Research Ethics Board and Children's and Women's Health Centre of British Columbia Research Review Committee.

RESULTS

Of the 594 women included in the retrospective study,[15] 295 were cared for at BC Women's; of these, 15 women (5.1%) developed the outcome. The postintervention cohort includes data from 405 women, of whom one was a postpartum transfer accompanying an infant admitted for neonatal intensive care.

Table 1 presents the clinical characteristics of the women in both cohorts. Initially, use of the standing orders for eligible antepartum women was 42%. For the final 15 months of the study period, the use

Table 1. Baseline Characteristics

Characteristic	Preintervention (n=295)	Postintervention (n=405)	*P* (Fisher or *t* Test)
Maternal age at EDD (y)	30.7 (30.0–31.4)	32.5 (31.9–33.1)	<.001
Gestational age on admission (wk)	36.0 (35.4–36.5)	35.1 (34.6–35.5)	.012
Early-onset disease (admission before 34^{+0} weeks of gestation)	99 (33.6)	128 (31.6)	.624
Multiple pregnancy (triplets: one set preintervention, two sets postintervention)	4 (1.4)	49 (12.1)	<.001
Parity: 1 or greater	86 (29.2)	104 (25.7)	.344
Smoking	26 (8.8)	31 (7.7)	.579
Corticosteroid administration	107 (36.3)	143 (35.3)	.811
Antihypertensive use	144 (48.8)	295 (72.8)	<.001
Magnesium sulfate use	152 (51.5)	186 (45.9)	.147
Blood pressure (mm Hg) (highest in first 24 h of admission)			
Mean arterial pressure*	121.5 (120.0–123.0)	125.1 (123.9–126.3)	<.001
Systolic blood pressure	160.4 (158.2–162.6)	168.8 (167.0–170.6)	<.001
Diastolic blood pressure	102.8 (101.5–104.1)	105.5 (104.5–106.4)	<.001
Dipstick proteinuria (+) (highest in first 24 h of admission)	1.55 (1.39–1.71)	2.49 (2.37–2.62)	<.001
AST (Units/L) (highest in first 24 h of admission)	78.8 (49.1–108.4)	76.3 (55.7–96.9)	.886
Platelets ($\times 10^9$/L) (lowest in first 24 h of admission)	189 (180–198)	191 (183–198)	.356
Admission to delivery interval (d) for admissions at all gestational ages	2.35 (1.73–2.97)	3.76 (3.04–4.48)	<.001
Admission to delivery interval (d) for women with early onset disease (admissions before 34^{+0} weeks of gestation)	4.68 (2.96–6.41)	7.90 (5.92–9.88)	.020
Gestational age at delivery (wk)	36.3 (35.8–36.8)	35.6 (35.2–36.0)	<.001
Birth weight (g)†	2,621 (2,499–2,743)	2,415 (2,318–2,512)	.009
SGA (birth weight less than third percentile)‡	16 (5.4)	34 (8.4)	.140

EDD, estimated date of delivery; AST, aspartate transaminase; SGA, small for gestational age.
Data are expressed as mean (95% confidence interval) or n (%).
* Mean arterial pressure is diastolic blood pressure+(pulse pressure/3).
† Birth weight assessed was that of the smallest fetus in a multiple pregnancy.
‡ For SGA, the pregnancy was deemed to have achieved the outcome if any one fetus was born at less than the third weight percentile for gestational age and gender.

remained consistently above 92% for antepartum women. Of the 404 women admitted antepartum for whom the orders were used, the minimum frequency of surveillance set by the standing orders was not met in 37 (9.2%) women, with 158 (39.1%) and 209 (51.7%) receiving surveillance either matching or exceeding the minimum frequency, respectively.

At all time periods, postpartum orders use remained about 10% lower than for the antepartum orders. The women in the postintervention cohort were at least as unwell with preeclampsia (in terms of objective blood pressure and renal and hepatic markers of disease severity) as the women in the preintervention cohort. Women in the postintervention cohort were also admitted at an earlier gestational age, were more likely to carry a multiple pregnancy, and more likely to receive antihypertensive medications than women in the preintervention cohort. Expectant management was more commonly used postintervention, as reflected in the increased admission-to-delivery interval for the whole postintervention cohort.

For women admitted before 34^{+0} weeks of gestation (when expectant management could be anticipated), the median admission-to-delivery interval was 2 days greater for the postintervention (128 of 405) than for the preintervention (99 of 295) cohort (4 days, interquartile range 2–9, compared with 2 days, interquartile range 1–3, respectively; Mann-Whitney *U*, $P<.001$).

Since the introduction of the standing orders, the incidence of the combined adverse maternal outcome fell from 5.1% (15 of 295) to 0.7% (3 of 405); Fisher exact test, $P<.001$; odds ratio 0.14 (95% confidence interval 0.04–0.49), with a power of 0.89 (Table 2). The combined adverse perinatal outcome did not differ between cohorts, but there was a trend to improved outcomes in the postintervention period (Table 3).

DISCUSSION

Introducing standing orders was associated with a reduced incidence of adverse maternal outcomes. This effect was greater than we had anticipated and than could have been expected from the experience

Table 2. Adverse Maternal Outcome

Outcome	Preintervention (n=295)	Postintervention (n=405)	*P* Fisher Exact	OR (95% CI)
One or more of maternal mortality or morbidity*	15 (5.1)	3 (0.7)	<.001	0.14 (0.04–0.49)
Maternal mortality	0 (0)	0 (0)	–	–
Maternal morbidities				
Hepatic				
Failure	2 (0.7)	0 (0)	.177	0.14 (0.01–3.03)
Hematoma/rupture	0 (0)	0 (0)	–	–
Central nervous system				
Glasgow coma score less than 13	1 (0.3)	0 (0)	.421	0.24 (0.01–5.97)
Stroke	2 (0.7)	0 (0)	.177	0.14 (0.01–3.03)
Cortical blindness	0 (0)	0 (0)	–	–
Two or more seizures of eclampsia	3 (1.0)	0 (0)	.074	0.10 (0.01–2.00)
Cardiovascular				
Positive inotrope support	1 (0.3)	1 (0.2)	.421	0.02 (0.01–5.97)
Infusion of third parenteral antihypertensive	3 (1.0)	0 (0)	.074	0.10 (0.01–2.00)
Myocardial infarction	2 (0.7)	0 (0)	.177	0.14 (0.01–3.03)
Renal				
Dialysis	0 (0)	0 (0)	–	–
Transplantation	0 (0)	0 (0)	–	–
Respiratory				
Requirement of 50% or more FIO_2 for more than 1 h	0 (0)	2 (0.5)	.512	3.66 (0.18–76.61)
Intubation (other than for cesarean delivery)	0 (0)	1 (0.2)	1.000	2.19 (0.09–54.03)
Hematological				
Transfusion of 10 Units or more of blood products	7 (2.4)	1 (0.2)	.012	0.10 (0.01–0.83)

OR, odds ratio; CI, confidence interval; FIO_2, fraction of inspired oxygen.
Data are expressed as n (%).
* Some women achieved more than one outcome (one woman achieved five).

Table 3. Adverse Perinatal Outcome

Outcome	Preintervention (n=295)*	Postintervention (n=405)*	*P* Fisher Exact	OR (95% CI)
One or more of perinatal mortality or morbidity	26 (8.8)	24 (5.9)	.181	0.65 (0.37–1.16)
Stillbirth	5 (1.7)	10 (2.5)	.602	1.47 (0.50–4.34)
Neonatal mortality†	5 (1.7)	5 (1.3)	.750	0.73 (0.21–2.55)
Perinatal morbidities†				
BPD	12 (4.1)	9 (2.3)	.183	0.54 (0.22–1.30)
IVH (grade 3 or 4)	0 (0)	0 (0)	–	–
cPVL	2 (0.7)	0 (0)	.179	0.15 (0.01–3.05)
NEC	7 (2.4)	2 (0.5)	.041	0.21 (0.04–0.998)
ROP (grade 4 or 5)	0 (0)	0 (0)	–	–

OR, odds ratio; CI, confidence interval; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; cPVL, cystic periventricular leukomalacia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.
Data are expressed as n (%).
* For all adverse outcomes, the pregnancy was deemed to have achieved the outcome if any one fetus did so.
† Of liveborn infants.

of others.[6] The women in the postintervention cohort were certainly not at lower risk than were those in the preintervention cohort; they had higher admission blood pressure, heavier admission dipstick proteinuria, and earlier-onset disease.[15] Twenty-four hour urines were collected in less than 60% of both cohorts; therefore, we cannot comment on the comparability of fully assessed proteinuria. We believe that the failure to routinely complete 24-hour collections was due to the fact that most cases of preeclampsia arise at term, and because those women are generally admitted for delivery, 24-hour urine collection is generally not practicable under those circumstances, even in a tertiary health sciences center. The maternal age differences and rising rates of multiple births (primarily through assisted reproductive techniques) observed between the cohorts reflect the changing maternity demographics seen in British Columbia.[25]

We recognize that combined adverse outcomes always reflect a spectrum of adversity.[26] For example, is the decision to use a third antihypertensive equivalent to the occurrence of stroke? This combined adverse maternal outcome was agreed upon by a Delphic consensus of internationally recognized experts in the field.[15] We believe that it is unusual for women to receive three parenteral antihypertensives (indeed, only 3 [0.43%] of the total 700 women did so). In this institution, this would reflect perceived clinical failure by the treating physicians (obstetrician, obstetric internist, and/or obstetric anesthesiologist) of both intravenous labetalol and hydralazine, precipitating the use of nitroprusside. We were not prescriptive of clinical practice, and no set guidelines were in place to guide the timing of the use of a third parenteral agent.

The improvements in outcome came during a phase of increasing institutional acceptance of expectant management of preeclampsia remote from term.[27] It might have been anticipated that increasing use of expectant management would be associated with increases, rather than decreases, in maternal morbidity,[28] because most practitioners await deteriorating maternal condition to precipitate the decision to deliver. We identified that women in the postintervention cohort admitted at less than 34^{+0} weeks of gestation had longer admission-to-delivery intervals than did those in the preintervention cohort, confirming our impression that local practice had changed. There was no change in adverse perinatal outcomes in the postintervention cohort (indeed the incidence of necrotizing enterocolitis was lower). Although there is the potential for a type II error, the trend toward a decrease in adverse perinatal outcome occurred in the postintervention cohort in which there was a lower gestational age at which the women were both admitted and delivered.

We were fortunate that the process of introducing a standardized pattern of assessment and surveillance for women admitted to a tertiary perinatal unit with either suspected or confirmed preeclampsia had the full support of the hospital administration and occurred through a stepwise process of feasibility study,[15] education (of medical, nursing, administration, and clerical colleagues), ongoing surveillance of implementation, and review of outcomes.

It is possible that the apparent success of introducing the standing orders may have accrued from the fact that they were not accompanied by management guidelines from the outset; a group of competent providers, when asked to collect data did not feel intimidated but did intervene more appropriately

when presented with a standardized data set. In comparison with the findings of Foy et al,[6] who found that the introduction of a complex set of guidelines was not effective in either altering practice or standardizing care, we chose to address a single element of the management of women admitted with the hypertensive disorders of pregnancy, namely their laboratory assessment and ongoing surveillance. The Yorkshire guidelines, which were introduced to guide the management of, rather than surveillance of, women with severe preeclampsia, have also been associated with reduced levels of maternal morbidity and rates of both between-hospital transfers and intensive care admissions.[29] Our experience with the standing orders is complementary to that of the Yorkshire group because our center is currently introducing management guidelines to the province of British Columbia in the context of a funded health services research project that will assess the manner of guideline introduction and the impact of those guidelines on outcomes across the province. These guidelines are based on those developed and introduced so successfully in Yorkshire and the standing orders. We believe that taking iterative steps will advance the quality of care more effectively than would trying to address all issues with a single large, and overwhelming, document addressing all aspects of care.

It is unclear what elements of the standing orders may have contributed to the fall in adverse maternal outcomes, although some have been identified through the retrospective study[15] and by others.[30] Certainly, before the introduction of the standing orders, the frequency and complexity of investigations varied between clinicians, as was predicted by our national review of practice.[1] We recognize that the number of tests in the current regimen is greater than that which is standard in most units. The identification of those elements of this standardized approach that are truly predictive of adverse maternal outcomes is occurring through an international study to develop an outcome prediction model for women with preeclampsia, the PIERS (Preeclampsia Integrated Estimate of RiSk) model. Once the PIERS model has been established, then a reduced list of investigations will be suggested to replace the current list that we recognize is probably overly thorough and, therefore, expensive.

The pattern of investigations has standardized the approach within our unit. The choice of follow-up surveillance testing being on Mondays and Thursdays was made to improve the timing of the delivery of infants away from times of reduced pediatric staffing, especially for those remote from term.[31] Of course, some or all of these investigations were performed at other additional times, at the discretion of the attending doctor or midwife; the influence of these "unscheduled" tests in the management of women with preeclampsia is a secondary outcome for the PIERS project.

A study limitation is that we do not have data on the eligible women who did not receive care using the standing orders during the postintervention phase of the study. In part, this is because we were aware of some women who were admitted with very severe preeclampsia and some end organ complications that evolved to become severe enough to fulfill the combined adverse maternal outcome. The physicians in these cases chose to write their own orders that almost matched the standing orders, but not fully. Therefore, we would have overly biased the analyses in favor of the standing orders.

In addition, we were underpowered to perform logistic regression analyses to determine the magnitude of any possible independent effect of the standing orders in influencing the change in outcomes. Although we have data on antihypertensive drug use in the retrospective cohort, we do not know the number of agents and duration of their use. Similarly, we do not have data on the rate of cesarean delivery in the preintervention cohort.

We recognize that the use of a preintervention and postintervention design is another significant limitation to this study. A better approach may have been to have randomized women to the use of guidelines or not. However, this methodology could not have been blinded, and we were concerned that the Hawthorne effect[32] would have been profound because women not randomized to the guidelines may have received significantly more detailed care than did those women who received care in our unit before the introduction of the guidelines. We are also reassured through the knowledge that the women in the postintervention cohort were at a comparable, if not greater, baseline risk on admission and received a greater degree of expectant management (Table 1).

Therefore, we conclude that carefully introducing and implementing standardized initial assessment and ongoing surveillance of women admitted to our hospital with preeclampsia has been associated with a reduced incidence of adverse maternal outcomes.

REFERENCES

1. Caetano M, Ornstein MP, von Dadelszen P, Hannah ME, Logan AG, Gruslin A, et al. A survey of Canadian practitioners regarding diagnosis and evaluation of the hypertensive disorders of pregnancy. Hypertens Pregnancy 2004;23:197–209.

2. Walker JJ. Severe pre-eclampsia and eclampsia. Baillieres Best Pract Res Clin Obstet Gynaecol 2000;14:57–71.
3. Androes MP, Kalbaugh CA, Taylor SM, Blackhurst DW, McClary GE Jr, GE Gray BH, et al. Does a standardization tool to direct invasive therapy for symptomatic lower extremity peripheral arterial disease improve outcomes? J Vasc Surg 2004;40:907–15.
4. Brown MM. Brain attack: a new approach to stroke. Clin Med 2002;2:60–5.
5. Bryce J, Gouws E, Adam T, Black RE, Schellenberg JA, Manzi F, et al. Improving quality and efficiency of facility-based child health care through Integrated Management of Childhood Illness in Tanzania. Health Policy Plan 2005;20 suppl:i69–76.
6. Foy R, Ramsay CR, Grimshaw JM, Penney GC, Vale L, Thomson A, et al. The impact of guidelines on mild hypertension in pregnancy: time series analysis. BJOG 2004;111: 765–70.
7. Furdon SA, Eastman M, Benjamin K, Horgan MJ. Outcome measures after standardized pain management strategies in postoperative patients in the neonatal intensive care unit. J Perinat Neonatal Nurs 1998;12:58–69.
8. Granger SR, Glasgow RE, Battaglia J, Lee RM, Scaife C, Shrieve DC, et al. Development of a dedicated hepatopancreaticobiliary program in a university hospital system. J Gastrointest Surg 2005;9:891–5.
9. Greenwald JA, McMullen HF, Coppa GF, Newman RM. Standardization of surgeon-controlled variables: impact on outcome in patients with acute cholecystitis. Ann Surg 2000; 231:339–44.
10. Gropen TI, Gagliano PJ, Blake CA, Sacco RL, Kwiatkowski T, Richmond NJ, et al. Quality improvement in acute stroke: the New York State Stroke Center Designation Project. Neurology 2006;67:88–93.
11. Hill MD, Barber PA, Demchuk AM, Sevick RJ, Newcommon NJ, Green T, et al. Building a "brain attack" team to administer thrombolytic therapy for acute ischemic stroke. CMAJ 2000; 162:1589–93.
12. Hirtenlehner K, Huber A, Strohmer H, Zeisler H, Husslein P, Langer M. Reduction of preeclampsia in multiple pregnancies by a dedicated monitoring protocol. J Soc Gynecol Investig 2003;10:418–22.
13. Smith S. Successful outcomes with the h.e.a.l. program. Ostomy Wound Manage 2006;52:40–2, 44, 46.
14. Zabek M, Zaczynski A. The golden hour and the dull reality. Analysis of traumatic brain injury management in pre-hospital and emergency care. Neurol Neurochir Pol 2007;41:22–7.
15. von Dadelszen P, Magee LA, Devarakonda RM, Hamilton T, Ainsworth LM, Yin R, et al. The prediction of adverse maternal outcomes in pre-eclampsia. J Obstet Gynaecol Can 2004;26:871–9.
16. Milholland AV, Wheeler SG, Heieck JJ. Medical assessment by a Delphi group opinion technic. N Engl J Med 1973;288: 1272–5.
17. Pill J. The Delphi method: substance, context, a critique and an annotated bibliography. Socioecon Plan Sci 1971;5:57–71.
18. von Dadelszen P, Magee LA, Marshall JC, Rotstein OD. The maternal syndrome of preeclampsia: a forme fruste of the systemic inflammatory response syndrome. Sepsis 2000;4:43–7.
19. von Dadelszen P, Magee LA, Lee SK, Stewart SD, Simone C, Koren G, et al. Activated protein C in normal human pregnancy and pregnancies complicated by severe preeclampsia: a therapeutic opportunity? Crit Care Med 2002;30:1883–92.
20. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183:S1–22.
21. Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J, et al. The detection, investigation and management of hypertension in pregnancy: full consensus statement. Aust N Z J Obstet Gynaecol 2000;40:139–55.
22. Helewa ME, Burrows RF, Smith J, Williams K, Brain P, Rabkin SW. Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. CMAJ 1997; 157:715–25.
23. Audibert F, Friedman SA, Frangieh AY, Sibai BM. Clinical utility of strict diagnostic criteria for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Am J Obstet Gynecol 1996;175:460–4.
24. Douglas KA, Redman CW. Eclampsia in the United Kingdom. BMJ 1994;309:1395–400.
25. British Columbia Reproductive Care Program. British Columbia Perinatal Database Registry Annual Report 2005. Available at: http://www.rcp.gov.bc.ca/newsletters/Annual%20Report%202005.pdf. Retrieved April 9, 2007.
26. Ross S. Composite outcomes in randomized clinical trials: arguments for and against. Am J Obstet Gynecol 2007;196: 119. e1–6.
27. Magee LA, Ornstein MP, von Dadelszen P. Fortnightly review: management of hypertension in pregnancy. BMJ 1999;318: 1332–6.
28. Olah KS, Redman CW, Gee H. Management of severe, early pre-eclampsia: is conservative management justified? Eur J Obstet Gynecol Reprod Biol 1993;51:175–80.
29. Tuffnell D, Jankowicz D, Lindow SW, Lyons G, Mason G, Russell I, et al. Outcome of severe pre-eclampsia in Yorkshire 1999/2003. BJOG 2005;112:875–80.
30. Martin JN Jr, May WL, Magann EF, Terrone DA, Rinehart BK, Blake PG. Early risk assessment of severe preeclampsia: admission battery of symptoms and laboratory tests to predict likelihood of subsequent significant maternal morbidity. Am J Obstet Gynecol 1999;180:1407–14.
31. Lee SK, Lee DS, Andrews WL, Baboolal R, Pendray M, Stewart S, et al. Higher mortality rates among inborn infants admitted to neonatal intensive care units at night. J Pediatr 2003;143:592–7.
32. Verstappen WH, van der Weijden T, ter Riet G, Grimshaw J, Winkens R, Grol RP. Block design allowed for control of the Hawthorne effect in a randomized controlled trial of test ordering. J Clin Epidemiol 2004;57:1119–23.

APPENDIX

The other members of the PIERS (Preeclampsia Integrated Estimate of RiSk) Study Group are Joanne Douglas, Mark Ansermino, Keith Walley, James Russell, Jelena Maric, and Daniela Caprera (Vancouver, BC); Jean-Marie Moutquin and Annie Ouellet (Sherbrooke, Québec); Graeme Smith (Kingston, Ontario); Andrée Gruslin (Ottawa, Ontario); James Walker (Leeds, UK); Philippa Kyle and Peter Moore (Christchurch, NZ); and Barry Walters (Subiaco, Western Australia, Australia).