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ORIGINAL ARTICLE

Utility of B-type natriuretic peptides in preeclampsia: a systematic review

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ABSTRACT
Background: Preeclampsia and its complications may be associated with elevated B-type natriuretic peptide levels during and after pregnancy.
Methods: We conducted a systematic review to determine whether preeclampsia and/or related cardiovascular complications, eclampsia and preterm delivery are associated with elevated natriuretic peptide levels. Three bibliographic databases were searched, using the terms ''natriuretic peptide'', ''pregnancy'', ''preeclampsia'', ''eclampsia'' and ''BNP''. Twelve studies fulfilled our inclusion criteria for full paper analysis. The data were too heterogeneous to allow for meaningful quantitative analyses.
Results: In healthy patients, B-type natriuretic peptide levels did not change during pregnancy. Compared with normal pregnancies, preeclamptic patients were shown to have significantly higher natriuretic peptide levels in the third trimester, which remained elevated for 3–6 months postpartum. Several papers suggested that cardiovascular dysfunction in preeclampsia is associated with NP elevation. Abnormalities were elevated systemic vascular resistance and cardiac filling pressures, decreased cardiac output, left ventricular diastolic dysfunction, and elevated left ventricular mass index. One investigation found that natriuretic peptide levels were higher in preeclamptic women who subsequently had preterm delivery, compared with those who delivered after 34 weeks. There were no data on natriuretic peptide levels in eclampsia.
Conclusions: Preeclampsia is associated with elevated natriuretic peptide levels. Cardiovascular complications and preterm delivery in this setting may also be associated with elevated natriuretic peptide levels. Large prospective studies of natriuretic peptide measurement in preeclampsia are needed to determine whether elevated levels predict the development of severe preeclampsia and/or associated complications.

Keywords: Preeclampsia; Natriuretic peptide; Brain; Cardiovascular complications; Pre-term delivery

Introduction

When exposed to myocardial stretch or ischaemia, cardiac myocytes release B-type natriuretic peptide (BNP), and its inactive N-terminal fragment cleavage product N-terminal pro B-type natriuretic peptide (NT-proBNP), into the blood. BNP is an independent predictor of mortality and cardiovascular events in several different patient populations.[1–6] Recently, small cases series have suggested that elevated levels of B-type natriuretic peptides (NPs) during pregnancy are associated with preeclampsia, cardiovascular morbidity, and preterm delivery.[7,8]

In the last two triennia, preeclampsia and eclampsia have been reported as the second highest direct cause of maternal mortality in the United Kingdom.[9] The Saving Mothers Report on Confidential Enquiries into Maternal Deaths in South Africa has shown that for the last decade, hypertension in pregnancy is the most frequent direct cause of maternal death.[10] Predicting major morbidity secondary to preeclampsia is difficult, and accurate risk stratification of high-risk obstetric patients would enable physicians to tailor obstetric care, surveillance, and delivery plans for these patients.

To better understand the association of elevated NPs in pregnancy with adverse outcomes, we undertook a systematic review to address the following questions:

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(1) Are NP levels significantly different between healthy obstetric patients and preeclamptic women? (2) Are elevated levels of NPs in preeclampsia associated with cardiovascular complications, eclampsia, or preterm delivery?

Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines were followed.[11] A registered review protocol does not exist for this systematic review. Ethics approval was not required for this systematic review.

All studies in which preeclamptic patients had NP measured before delivery were considered eligible. Studies were included regardless of language, sample size, and publication status. Where studies collected relevant data but did not report the outcomes of interest, we contacted the authors to obtain the relevant outcome information.

To identify eligible studies, we searched three bibliographic databases (MEDLINE, EMBASE, and Cochrane databases from 1966 to week 29 of 2011), reviewed our own files and reference lists from eligible studies, and consulted with experts. We used the following terms and combinations of terms for the database searches: ''natriuretic peptide'', ''BNP'', ''pregnancy'', ''eclampsia'' and ''preeclampsia''.

Two authors (NA and AB) independently screened the title and abstract of each citation to identify all studies that could fulfil the eligibility criteria. Those studies which were considered potentially eligible then underwent full text review to confirm eligibility. If disagreements occurred during the full text review, these were resolved through independent adjudication by a third reviewer (BB). Study quality was not considered during this process.

The following descriptive data were abstracted from all eligible studies: year of publication, study design, sample size, type of NP assay used, time of NP sampling, and outcomes reported. The following criteria were evaluated to assess the quality of the included studies: number of patients lost to follow-up, blinding of data collectors and outcome assessors to BNP values, and whether the outcome assessment was the same for all study participants. We modified the Cochrane Group recommendations for systematic reviews of diagnostic test accuracy for assessment of study quality (Appendix 1).[12] Outcomes included the diagnosis of preeclampsia, eclampsia, cardiovascular complications and preterm delivery. Cardiac failure, cardiac dysfunction (as defined in included studies), cardiac arrest, and cardiac arrhythmias were included under the definition of cardiovascular complications.

Two authors (BB and RR) independently abstracted data into a standardised spreadsheet from all studies fulfilling the eligibility criteria. Disagreements were resolved through consensus, and where necessary through independent adjudication (RD). If required, we contacted study authors to obtain missing data and confirm abstracted data.

Statistical Analysis

As there were marked differences between the retrieved studies with respect to inclusion criteria, sampling times, assays used and outcome definitions, we have not presented a quantitative analysis of the data extracted. Odds ratios (OR) and 95% confidence intervals (CI) have been presented where appropriate.

Results

The literature search identified 321 studies, of which 22 were identified for full paper analysis. Of these 22 studies, 12[7,8,13–22] fulfilled our inclusion criteria (Fig. 1).

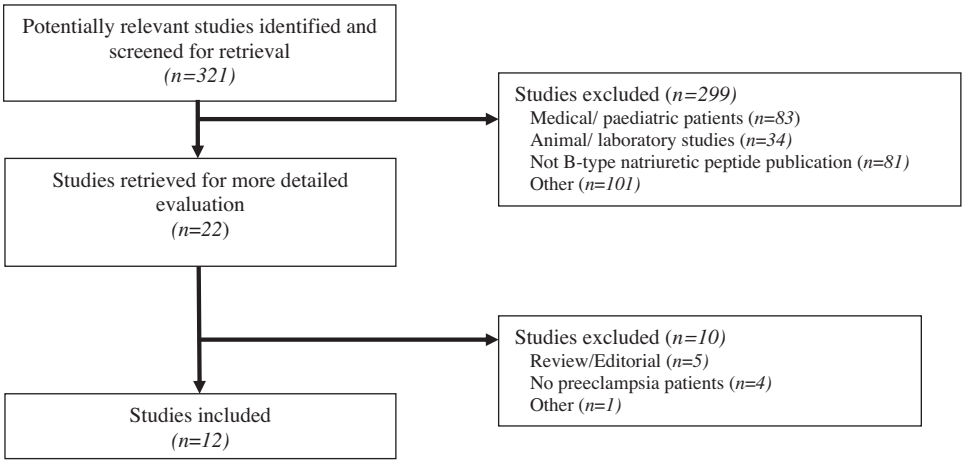

Fig. 1 PRISMA flow diagram of study identification.

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Table 1 Characteristics of eligible studies

	Type of observational study	Mean patient age (years)	No. of preeclamptic patients	Patient population	Adverse outcome data available	Study definition of adverse outcome
Kaaja (1999)[13]	Prospective	30	9	Elective	NR	NR
Borghi (2000)[14]	Prospective	31.4	40	Elective	LV overload	Markers of LV mass and volume
Fleming (2001)[15]	Prospective	28.5	6	Elective	NR	NR
Folk (2005)[16]	Retrospective	NR	7	Urgent	Ventricular systolic dysfunction, Ventricular diastolic dysfunction	Congestive cardiac failure with poor systolic function "Flash pulmonary oedema"
Kale (2005)[17]	Prospective	29.6	40	Elective	NR	NR
Resnik (2005)[18]	Prospective	27.4* 29.9†	34	Elective and urgent	Severe preeclampsia	SBP $\geqslant$160 mmHg or DBP $\geqslant$110 mmHg $\pm$ organ involvement based on consensus ccriteria
Tihtonen (2007)[19]	Prospective	33	19	Elective	Bio impedance- derived cardiovascular parameters	Significant correlation between SVRI and NT-proBNP ($p = 0.04$)
Rafik Hamad (2009)[20]	Prospective	31	35	Elective	Diastolic dysfunction, left atrial enlargement Preterm delivery	LVMI < 66 g/m^2 Delivery before 34 weeks
Fustaret (2010)[21]	Prospective	NR	20	Elective and urgent	Systolic dysfunction Abruptio placenta	NR
Moghbeli (2010)[7]	Prospective	27.5	63	Elective and urgent	Severity of preeclampsia Preterm delivery	Mild and severe preeclampsia according to ACOG definitions Delivery before 34 weeks
Speksnijder (2010)[8]	Prospective	25	22	Urgent	HELLP syndrome PAC- measured haemodynamic parameters	Serum ALT and AST >30 U/L, platelet count $<100 \times 10^9$/L, haemolysis on peripheral smear.
Tanous (2010)[22]	Prospective	31	6‡	Elective and urgent	Adverse maternal cardiac and fetal/ neonatal events – for women with structural heart disease Ventricular dysfunction	Maternal death, heart failure and arrhythmias. Fetal death, premature birth, LBW

NR: not reported; LV: left ventricle; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVMI: left ventricular mass index; SVRI: systemic vascular resistance index; NT-proBNP: N-terminal pro B-type natriuretic peptide; ACOG: American College of Obstetricians and Gynecologists; HELLP: haemolysis, elevated liver enzymes and low platelets; PAC: pulmonary artery catheter; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LBW: low birth weight.* Severe preeclampsia.; † Mild preeclampsia.; ‡ Pregnancy induced hypertension (PIH).;

Table 2 Characteristics of B-type natriuretic peptide assays and sampling

	Biomarker	Diagnostic assay	Gestational age when natriuretic peptides sampled (weeks)	Laboratory reference limit used in the study (pg/mL)
Kaaja (1999)[13]	BNP	NR	37.4	NR
Borghi (2000)[14]	BNP	Nycomed Amersham	28.4	20
Fleming (2001)[15]	NT-proBNP	Biomedica, Vienna	35	NR
Folk (2005)[16]	BNP	Triage (Biosite Diagnostics Inc)	Variable	100
Kale (2005)[17]	NT-proBNP	Roche	34	NR
Resnik (2005)[18]	BNP	Triage (Biosite Diagnostics Inc)	32.2	40
Tihtonen (2007)[19]	NT-proBNP	NR	33	86
Rafik Hamad (2009)[20]	NT-proBNP	Roche Diagnostics	35	150
Fustaret (2010)[21]	NT-proBNP	NR	33	125
Moghbeli (2010)[7]	NT-proBNP	Dade Behring Dimension Vista	37	NR
Speksnijder (2010)[8]	NT-proBNP	Elecsys (Roche)	37	NR
Tanous (2010)[22]	BNP	Fujirebio Diagnostics, Inc	1st, 2nd and 3rd trimester	100

NR: not reported; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide.

Table 3 Key study quality characteristics of included investigations

	Blinded NP assessment	Blinded adverse outcome assessment	Consistent outcome assessment	Method of patient follow-up	Study quality[12] (out of 8)*
Kaaja (1999)[13]	No	NR	NR	NR	4
Borghi (2000)[14]	No	No	Yes	NR	4
Fleming (2001)[15]	No	No	No	NR	4
Folk (2005)[16]	No	No	Yes	NR	5
Kale (2005)[17]	No	No	NR	NR	4
Resnik (2005)[18]	No	No	NR	Sequential samples until delivery	4
Tihtonen (2007)[19]	No	No	Yes	NR	4
Rafik Hamad (2009)[20]	No	No	Yes	Clinic	7
Fustaret (2010)[21]	No	No	Yes	Postpartum samples taken but no details reported	6
Moghbeli (2010)[7]	No	No	NR	NR	4
Speksnijder (2010)[8]	No	No	Yes	NR	3
Tanous (2010)[22]	No	No	Yes	Clinic up to 6 months	7

NP: natriuretic peptide; NR: not reported.* See Appendix 1 for study quality criteria.;

Additional data necessary for analysis were obtained from the authors of three investigations.[8,19,20] Fig. 1 demonstrates the abstracts and articles identified and evaluated during the review process.

The characteristics of the included publications are shown in Table 1. Eleven of the 12 studies were prospective. Details of the biomarker assays are shown in Table 2. Five studies measured BNP and seven measured NT-proBNP. Most investigators sampled NPs only in the third trimester; only two studies measured NPs in all three trimesters.[18,22]

The study quality characteristics are shown in Table 3. In general the quality was poor, with eight of the 12 investigations only scoring 4 out of 8 on the modified study quality assessment tool (Appendix 1).[12] Only two high-quality studies were identified, with scores of 7.[20,22]

Preeclampsia and B-type natriuretic peptide levels

Two studies reported BNP levels in normal pregnant women in the first, second and third trimesters.[18,22] BNP levels did not change through pregnancy, with a median level of <20 pg/mL throughout pregnancy in one study,[18] and a median peak level of 35 pg/mL (interquartile range 21–43 pg/mL) in the other.[22] Two investigations reported an association between preeclampsia and NP elevation above the study NP reference limit, compared with normotensive controls.[19,20] Although both studies measured NT-proBNP, the laboratory reference limits differed between the two investigations, and hence the data could not be combined. One high-quality study showed significantly more preeclamptic patients above the upper reference limit (OR 30.7, 95% CI 3.8–251)[20] and the other investigation showed a trend towards NT-proBNP elevation (OR 21, 95% CI 0.5–

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192).[19] In seven of eight studies identified, preeclamptic patients were shown to have significantly higher NP levels in comparison with normal parturients in the third trimester.[7,14,15,17–20] In addition, one investigation found that NP levels were significantly higher in preeclamptic patients than in chronic hypertensive pregnant patients.[19] NP levels remained elevated at three to six months post-delivery, in comparison with normal pregnant controls.[20] A single publication did not report a difference in NP levels between matched "mild" preeclamptic patients and healthy control pregnant patients at 37 weeks of gestation.[13]

Cardiovascular complications in preeclampsia, and elevated B-type natriuretic peptide levels

Five investigations reported the association between preeclampsia, cardiovascular dysfunction and NP levels.[8,14,16,19,20] In a high-quality study comparing preeclamptic women and healthy parturients, several echocardiographic features of left ventricular diastolic dysfunction were associated with NP elevation. However, only left ventricular mass index was independently associated with NP elevation, both in the overall group,[20] and within the preeclamptic cohort (personal communication, Dr R. Rafik Hamad). Another study showed that in a group of preeclamptic patients, a BNP cut point above 20 pg/mL was associated with significantly increased left ventricular mass, and left ventricular end systolic and diastolic volumes.[14] Pulmonary capillary wedge pressure and pulmonary diastolic pressures were correlated with NP levels in untreated preeclamptics.[8] One investigation found that in both treated and untreated preeclamptic patients, NP levels were correlated with the systemic vascular resistance (SVR) and inversely correlated with the cardiac index (CI).[19] In a low-quality, retrospective investigation with a small sample size ($n = 2$ for preeclamptic patients), a trend towards congestive cardiac failure was shown.[16] A further study which grouped preeclamptic and valvular heart disease patients, reported that a BNP level <100 pg/mL had a 100% negative predictive value for adverse cardiac events during pregnancy, and a sensitivity and specificity of 100% and 70% respectively.[22] The high negative predictive value should be interpreted with caution, since the study numbers were small, and patients with heart disease represented a heterogeneous group. Individual data for preeclamptic patients could not be obtained from the authors.

In summary, the literature suggests that elevated SVR and cardiac filling pressures, echocardiographic features of left ventricular diastolic dysfunction, and depression of cardiac output in preeclamptic patients are all associated with elevated NP levels. In addition, marked NP elevations may be associated with patients at risk of rapid systolic decompensation.[16] The relationship between NP levels and cardiovascular dysfunction may be modified by fluid and pharmacotherapy, although there are few data in the literature to inform this issue.[19]

Eclampsia and elevated B-type natriuretic peptide levels

No study reported an association between elevated NPs and progression to eclampsia. One investigation examined preeclamptic patients who developed HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome.[8] Data from the authors revealed no association between elevated NPs and HELLP syndrome (OR 0.83, 95% CI 0.12–6.0), although the sample size ($n = 22$) was small. Another small study, from which we could not obtain further data, reported a correlation between NT-proBNP and platelets, alkaline phosphatase and proteinuria.[21]

Preterm delivery in preeclampsia, and B-type natriuretic peptide levels

Two investigations reported the association between NP levels and preterm delivery in preeclampsia.[7,20] In a high-quality study, NP levels were significantly higher in electively-admitted preeclamptic women who subsequently had preterm delivery, compared with those who delivered after 34 weeks.[20] This was not shown in a low-quality investigation which included both elective and urgent admissions for preeclampsia.[7]

Discussion

In this systematic review, most investigations, generally of a small size, have shown that preeclampsia is associated with elevated NP levels. There are insufficient data to confirm that further elevated NP levels in preeclamptic patients identify those at risk for cardiovascular complications or preterm delivery, although the studies identified suggest that this requires further investigation. There are no available data to determine whether eclampsia is associated with elevated NP levels.

The diagnosis of severe preeclampsia is based upon well-defined criteria such as elevated blood pressure, proteinuria, and complications such as pulmonary oedema, HELLP syndrome, renal failure, and eclampsia.[23,24] As a result of these complications, mothers with severe preeclampsia have a high mortality risk.[9,25] Perinatal mortality risk is also high because of intrauterine growth restriction, preterm delivery, and abruptio placentae.

Recently, von Dadelszen et al. used a combination of clinical and laboratory factors to identify which preeclamptic women were at high risk of developing fatal or life-threatening complications. The authors identified gestational age, chest pain or dyspnoea, oxygen saturation, platelet count, creatinine and aspartate

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transaminase concentrations as significant predictors in the model.[26] However, other authors have cautioned that in the latter study, a large number of predictors were used for a relatively small number of events.[27] Indeed, early work showed that the incidence of pulmonary oedema in severe preeclampsia is relatively low (overall 2.9%, with 30% of these cases occurring antepartum and 70% postpartum).[28] This is in agreement with the recent study on risk prediction, which found an incidence of 3%.[27] A further limitation of the model described by von Dadelszen et al. is that many of the factors, such as chest pain, dyspnoea, and oxygen desaturation, although very important clinical signs, are late presentations of severe preeclampsia and herald the imminent development of life-threatening complications. These late clinical warning signs may not provide sufficient time for physician intervention. In light of these observations, an obstetric ''early warning system'' for preeclampsia and severe preeclampsia is desirable, and this systematic review suggests that the measurement of NP levels may be of benefit. Indeed, recent data have shown that NPs are significantly better than traditionally-used clinical risk factors, at predicting major adverse cardiac events following non-cardiac surgery.[26]

In healthy parturients, NP levels are not expected to change through pregnancy.[18] However, in pregnancies complicated by preeclampsia, there appears to be a graded increase in NP levels with increasing severity of the disease.[7,18] This systematic review confirms that preeclampsia is associated with higher NP levels than those measured in healthy parturients, and suggests that cardiovascular complications and preterm delivery in preeclamptic women may be associated with further elevated NP levels. Thus, it is possible that NP measurement during pregnancy may have the potential to identify these high-risk patients earlier along the path of their disease progression.

NP levels are elevated in left ventricular systolic and diastolic dysfunction, and heart failure in the non-obstetric population.[29] Our systematic review suggests that NP levels may also be of clinical utility in identifying preeclamptic women at risk of cardiovascular complications. Echocardiographic features of diastolic dysfunction are well described in the non-obstetric population,[30] as well as in preeclampsia,[31–33] and transthoracic echocardiography is increasingly being employed in obstetric critical care.[34] It is possible that measurement of NP levels may increase the sensitivity and specificity of clinical and echocardiographic prediction of the development of cardiovascular complications such as pulmonary oedema in preeclamptic patients. Ultimately NP cut-off values may be determined to more accurately predict this risk, as has already been shown in the non-obstetric literature.[35]

Preeclamptic women are also at a significantly increased risk of chronic hypertension and ischaemic heart disease.[36] NP levels have shown utility in predicting long-term cardiovascular complications and may be useful in the risk stratification of preeclamptic patients after delivery.[37] This is a field of obstetric care which needs further study.

The number of investigations included in this systematic review, as well the number of patients in each study is small. Furthermore, the inclusion criteria of the patients, the timing of NP evaluation relative to therapeutic interventions, the different assays and laboratory reference limits, and the difference in outcome definitions made it inappropriate to combine the data in a meta-analysis.

This systematic review shows that preeclampsia is associated with elevated NP levels, and suggests that cardiovascular complications and preterm delivery in preeclampsia may be associated with further elevated levels. Further larger prospective, observational studies are required to establish whether there is an association between NP levels and these complications. Such studies would need to control for the time of inclusion, the severity of the preeclampsia, and the relationship to any therapeutic interventions, if they are to provide a test of high sensitivity and specificity for the prediction of cardiovascular and other complications associated with preeclampsia. The prognostic utility of NP levels in determining outcome in preeclampsia, in combination with clinical and echocardiographic findings, remains to be established.

Disclosure

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Appendix 1. Study quality assessment[12]

1. Were the patients representative of the patients who will receive the test in practice? (i.e. did the study patients have preeclampsia?)
2. Is the reference standard likely to classify the target condition correctly? (i.e. did the study use the internationally accepted diagnostic criteria for preeclampsia?)
3. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? (i.e. acceptable delay between tests)
4. Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? (i.e. partial verification avoided)
5. Did patients receive the same reference standard irrespective of the index test result? (i.e. differential verification avoided- was the diagnosis of preeclampsia consistent irrespective of the natriuretic peptide results)
6. Was the reference standard independent of the index test (i.e. natriuretic peptides were not used in the diagnosis of preeclampsia)
7. Were the reference standard results interpreted without knowledge of the results of the index test? (i.e. blinding as to natriuretic peptides results in the diagnosis of preeclampsia)
8. Were the index test results interpreted without knowledge of the results of the reference standard? (i.e. natriuretic peptides interpreted blind with respect to the diagnosis of preeclampsia)
9. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? (i.e. relevant clinical information)
10. Were uninterpretable/intermediate test results reported? (i.e. uninterpretable results reported)
11. Were withdrawals from the study explained?
12. *For the purposes of this prognostic survey we considered questions 3, 4 and 10 not applicable, and these were not considered in the study quality assessment.*

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