Title: Hypertension Management During Pregnancy: Could We Do Better?

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ajo.12499](https://doi.org/10.1111/ajo.12499)

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Acknowledgements

We would like to thank Denise van den Bosch for assistance with data entry and the Health Information Services team at the Mercy Hospital for Women for retrieving the medical records. We acknowledge Andre Francis and Professor Jason Gardosi for help with the customised centiles.

Received Date : 29-Apr-2015

Revised Date : 31-Mar-2016

Accepted Date : 29-May-2016

Article type : Original Manuscript

Title: Management of pregnancies complicated by hypertensive disorders of pregnancy: Could We Do Better?

Short Title: Hypertension During Pregnancy: Could We Do Better?

Word count of text: 2680

Word count of abstract: 256

Tables: Four

Figures: Two

Keywords: low-dose aspirin, HYPITAT, SOMANZ, gestational hypertension, chronic hypertension

Abstract

Background: Hypertensive disorders are among the most common medical problems in pregnancy. Compliance with clinical practice guidelines has potential to translate to significant maternal and perinatal health benefits.

Aims: To evaluate compliance with Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) clinical guidelines for management of hypertension during pregnancy.

Methods: Inclusion criteria: women with hypertension in pregnancy who gave birth at a tertiary obstetric centre in 2010. Compliance with SOMANZ guidelines was assessed, as well as uptake of findings from the 'Induction of labour versus expectant monitoring for mild gestational hypertension/pre-eclampsia after 36 weeks' gestation' (HYPITAT) trial.

Results: 516/5,624 women (9.2%) were identified with hypertension (49 CH; 457 GH or PE). Thresholds to diagnose hypertension and initiate anti-hypertensive treatment were consistent with SOMANZ recommendations. Among women with CH, only 12.2% were prescribed aspirin prior to 16 weeks as PE prophylaxis. Of women with PE, 37 (18.6%) had known risk factors for development of PE at the initial visit yet only 9 (24.3%) received aspirin. Of the 244 women who met HYPITAT inclusion criteria at 36 weeks, 174 (77.7%) were managed expectantly; 9 (5.2%) developed severe adverse outcomes.

Conclusion: Current management guidelines for hypertension treatment were generally followed, although aspirin prophylaxis was frequently overlooked, resulting in up to 19 excess PE cases. Uptake of recommendations from the HYPITAT trial was low; however, severe complications were fewer than expected. Overall, this suggests that clinicians appropriately weigh up the likely maternal risk compared to infant benefits of deferred delivery in each case, a key recommendation of HYPITAT-II.

Introduction

Hypertensive disorders, a leading contributor to maternal mortality and morbidity, complicate approximately 10% of pregnancies in Australia.¹ Perinatal risks of maternal hypertension include fetal growth restriction [FGR] and premature birth, with attendant increase in morbidity and mortality.¹ The legacy of preterm birth and FGR is lifelong, with increased risks of neonatal and childhood morbidity, and increased health risks in adulthood.²

Optimising the management of hypertensive disorders in pregnancy is an important component of antenatal care. At the time of this study, the 2008 Society of Obstetric

Medicine of Australian and New Zealand [SOMANZ] guidelines on management of hypertension in pregnancy were in use,³ on which our institutional guideline for management of hypertension in pregnancy was based. In 2014, the SOMANZ guidelines were updated.⁴ Key recommendations include use of aspirin with or without calcium to reduce the risk of pre-eclampsia [PE] in moderate to high-risk women; attention to blood pressure control and surveillance for development of superimposed PE and FGR. Clear endpoints have been identified for delivery in severe PE. These recommendations have largely been unchanged since the publication of the 2008 guidelines (Table 1),³ with the exception of the threshold for treatment of severe hypertension and the timely delivery of women with mild-moderate hypertensive disease, in light of findings from the 'Induction of labour versus expectant monitoring for gestational hypertension or mild PE after 36 weeks gestation' [HYPITAT] trial.⁵

Aims

- (i) To evaluate compliance with SOMANZ 2008 clinical guidelines⁴ for management of hypertension during pregnancy, specifically:
 - a) thresholds for initiation of anti-hypertensive therapy;
 - b) appropriateness of medication regimens;
 - c) use of aspirin in women with known risk factors for development of PE;
- (ii) To evaluate clinical uptake of findings from the HYPITAT⁵ trial regarding induction of labour for women with gestational hypertension [GH] or PE at term; and
- (iii) To describe obstetric and neonatal outcomes in women with chronic hypertension [CH], GH and PE according to anti-hypertensive treatment.

Methods

Antenatal records were electronically retrieved for women who gave birth in 2010 at the Mercy Hospital for Women and had an International Classification of Diseases (ICD)-10 code⁶ recorded for any hypertensive disorder during pregnancy. The diagnostic criteria for GH, CH and PE were based on the SOMANZ 2008 guidelines.³ Records were manually reviewed (by AH) and relevant data were extracted. Maternal data included demographics, medical and obstetric history, progression and management of hypertension, including development of: moderate to severe hypertension (systolic BP ≥ 150 -170 mmHg and/or

diastolic BP $\geq 100 - 110$ mmHg),³ severe hypertension (systolic BP ≥ 170 mmHg and/or diastolic BP ≥ 110 mmHg),³ and PE.³ Use of aspirin and time of initiation were recorded. Neonatal data included gestational age at delivery, birthweight and need for special or neonatal intensive care admission. Customised centiles were calculated and FGR recorded if birthweight was less than the 10th customised centile. Centiles were calculated using the calculator devised by Mongelli et al⁷ specifically for the Australian population, allowing adjustment for maternal characteristics such as height and weight, gestational age and fetal gender.

Among women who reached 36 weeks gestation with mild GH or PE and a single fetus in a cephalic presentation, outcomes were compared between those managed expectantly and those managed with immediate/as soon as practicable induction of labour [IOL], as described in the HYPITAT trial.⁵ Outcomes compared between groups were those reported in HYPITAT, namely maternal mortality, maternal morbidity (eclampsia; Haemolysis, Elevated Liver enzymes and Low Platelets [HELLP] syndrome; pulmonary oedema; thromboembolic disease; and placental abruption), progression to severe hypertension or proteinuria, and major post-partum haemorrhage (>1000 mL blood loss).⁵

Data were analysed using descriptive statistics and appropriate univariate analysis (one way ANOVA, Kruskal-Wallis, Mann-Whitney U tests and Student's t-tests) using SPSS (version 21.0, IBM, New York). $P < 0.05$ was considered statistically significant. Post-hoc comparisons were done using Bonferroni test. Human Research Ethics Committees of Mercy Health and Monash University approved the study.

Results

Of the 5624 women who gave birth at MHW in 2010, 602 (10.7%) had an ICD code for hypertension. Of these, 86 were excluded as they did not meet the SOMANZ criteria for hypertension in pregnancy (Figure 1). The number of women included in the analysis was 516, resulting in 524 babies (8 sets of twins). Participants were classified into groups: CH (treated and untreated) ($n = 49$); GH (treated and untreated) ($n = 268$) and PE ($n = 199$). The CH treated group includes women with CH who were receiving treatment during pregnancy regardless of initiation pre-pregnancy or during pregnancy. The CH untreated group includes those who did not receive treatment at any time during pregnancy. Demographic and obstetric details are summarised in Table 2.

Management of pregnancies at term (36 weeks and beyond) with mild hypertension during pregnancy

Of the 355 women with mild GH or mild PE, 224 (63.1%) had not been delivered at 36 weeks and had no contraindication for IOL, such as breech or planned caesarean. Of these, 50 (22.3%) were managed with immediate/as soon as practicable IOL, while 174 (77.7%) were managed expectantly. Progression to severe hypertension and to severe PE were the only relevant adverse outcomes in this group. The proportion of women who developed a composite severe adverse outcome, as defined by HYPITAT,⁵ was 4.0% in the immediate management group and 5.2% in the expectant management group, rates that were not significantly different. There was no significant difference in the rate of caesarean section between these groups. The FGR (<10th centile) rate was 9.2% in the expectant management group and 14% in the immediate management group. There was however no significant difference in the customised centile between the two groups (44.9 [$\pm$ 28.7] and 49.6 [$\pm$ 30.4] in the immediate and expectant management groups, respectively).

Thresholds for diagnosis of hypertension and initiation of treatment

Treatment was initiated at mean systolic BP 154mmHg and diastolic BP 97mmHg. BP at initiation of treatment did not differ among the three groups (Table 3). Women prescribed treatment for hypertension (with GH or PE; n=125), were more likely not only to be diagnosed at higher systolic and diastolic BP, but also at an earlier gestation than those with untreated GH or PE.

Medication prescribing patterns for hypertension during pregnancy

Among women with CH, methyldopa was first-line treatment in 62.5%, followed by labetalol in 31.3%. Other agents included nifedipine, phenoxybenzamine and metoprolol XL. Three (9.4%) required multiple anti-hypertensive agents. Among women with GH, labetalol was first-line treatment in 79%, followed by methyldopa in 13.8%. Two (6.9%) were prescribed nifedipine as an additional agent. Among women with PE, labetalol was prescribed in 71.4% and methyldopa in 59.1%. Twenty-five (37.9%) required multiple antihypertensive agents; 13.7% were treated with other agents, including nifedipine, hydrazaline, verapamil and magnesium sulphate.

Use of low-dose aspirin and/or calcium in women with moderate to high risk of pre-eclampsia

Of the 49 women who had CH at the initial visit, only six (12.2%) received low-dose aspirin, two of whom also received calcium supplementation, at gestation < 16 weeks (Table 2). Two women commenced aspirin after 16 weeks. Mean gestation at initiation of therapy was 10 weeks 3 days. Of those who developed hypertension during pregnancy (GH and PE), 65 (13.9%) had an indication for low-dose aspirin at the initial visit, most commonly past history of PE (84.6%), renal disease (3.1%), systemic lupus erythematosus (4.6%) or family history of PE (3.1%). Of these, only 15 women (23.1%) were prescribed low-dose aspirin, at a mean gestational week of 13 weeks 6 days. Of the total 114 women with a recognised risk factor in this cohort, 38 (33.3%) developed PE, 26 of whom were not prescribed aspirin. Three women (3.2%) in the group who were not prescribed aspirin developed early-onset severe PE (including one with HELLP). Six (28.6%) women who were prescribed aspirin developed early onset or severe PE, including three with HELLP.

Obstetric and neonatal outcomes

The mode of delivery for women from each group is shown in figure 2. The number of women who had delivery for suspected compromise were: CH untreated (1; 5.9%), GH untreated (11; 4.6%), GH treated (2; 6.9%); and PE (2; 1.0%). Neonatal outcomes are summarised in Table 4.

Eighty-six women developed severe hypertension during their pregnancy: three (17.6%) CH untreated, 13 (5.4%) GH untreated, 6 (18.8%) CH treated, 9 (31.0%) GH treated and 55 (27%) PE; of these, 65 progressed from mild-moderate hypertension to severe hypertension; 37 (56.9%) of whom were prescribed antihypertensive medication. One hundred and thirty-five (56.5%) women with untreated GH progressed to mild or severe PE or HELLP, compared to 49/78 (62.8 %) of those prescribed an antihypertensive. Fifteen women (23.4%) with CH progressed to at least mild PE. There were two incidences of placental abruption in women who had severe PE, neither of whom was prescribed antihypertensive medication or aspirin. The mean gestational age at delivery for the total cohort was 38 weeks and 1 day (± 16 days) (Table 4).

There were two perinatal deaths. One case presented with fetal death-in-utero at 38 weeks and was later diagnosed with severe hypertension; the second occurred in the context of severe mid-trimester FGR and PE. The most frequent perinatal complication across the groups was FGR, indicated in table 4.

Discussion

Our study shows that clinical guidelines for women with hypertension are largely being followed, although there is potential for improvement in compliance with prescription of aspirin prophylaxis for the prevention of PE. This study also reports a low incidence of major adverse events, suggesting that clinician compliance with institutional and SOMANZ clinical guidelines is safe and effective. In this cohort, it was common for near term hypertension to be managed expectantly contrasting data from the United States in the same timespan.⁸ Less than one quarter of 'HYPITAT eligible' patients were delivered at 37 weeks, yet we observed a lower rate of adverse maternal outcome in this group than would have been predicted by HYPITAT. In part, this is because expectant management for this cohort was not prescribed by the HYPITAT endpoints, i.e. delivery at 41 weeks unless severe hypertension or proteinuria, eclampsia, HELLP syndrome, fetal distress, and prelabour rupture of membranes supervenes. The SOMANZ guidelines advise considering delivery after 37 weeks, particularly if maternal or fetal complications have developed. Many patients in this study were therefore managed expectantly until after 37- but prior to 41- weeks, which may explain some of the observed differences in major adverse events in this cohort compared to HYPITAT. This suggests that clinicians are actively weighing up the potential maternal benefit of immediate delivery versus neonatal harm, including the long term consequences of late preterm and early term birth, which are being increasingly recognised.⁹⁻¹² HYPITAT-II has specifically addressed this: among women with mild GH or PE between 34-37 weeks, expectant management was associated with a small and non-significant increase in maternal adverse outcomes, but a significant reduction in neonatal respiratory distress, leading the authors to conclude that delivery should be deferred until 37 weeks, unless maternal deterioration supervenes.¹³

BP levels for diagnosis of hypertension, thresholds at which anti-hypertensive medication were initiated, and choice of antihypertensive were consistent with both the 2008 and 2014 SOMANZ guidelines.^{3,4} The majority of women who had CH were initiated on antihypertensive medication prior to pregnancy by their general practitioner, which continued throughout pregnancy. Choice of anti-hypertensive medication across the cohort was appropriate, the majority being initiated on labetalol during pregnancy. The higher proportion of methyldopa prescriptions in the CH treated group suggests that general practitioners remain more familiar with methyldopa than labetalol as a first line agent, despite the demonstrable safety, better tolerance and efficacy of the latter in preventing progression to

severe hypertension.¹⁴ A Canadian study of prescribing for hypertension during pregnancy by general practitioners reported similar prescribing patterns.¹⁵

The appropriate threshold for initiating antihypertensive therapy remains unclear. There is an undisputed need for treatment of severe hypertension (BP $\geq 160/110$ mmHg).⁴ The Centre for Maternal and Child Enquiries in the UK recommends including the treatment of a systolic BP of ≥ 150 mmHg as one of its top 10 recommendations.¹⁶ A recent systematic review was inconclusive regarding the benefits of treatment of mild-moderate hypertension during pregnancy, confirming that treatment of mild-moderate hypertension does not influence progression to PE.¹⁴ The recently published Control of Hypertension In Pregnancy Study (CHIPS)¹⁷ found no significant differences in the risk of pregnancy loss, high-level neonatal care or overall maternal complications between less-tight (target diastolic BP 100 mmHg) versus tight (target diastolic BP 85 mmHg) control of hypertension. There was, however, an observed higher incidence of severe hypertension in the less-tight group. While this study was expected to inform the debate regarding treatment of mild-moderate hypertension, it seems likely that treatment will continue to be dictated by local clinical practice and individual prescribing patterns.

While PE was more common in the GH treated group, PE also complicated 36% of cases whose hypertension was not severe enough to require treatment, confirming that these women needed to remain under close surveillance. In this cohort, all women who developed hypertension were referred to the Pregnancy Assessment Day Centre after initial diagnosis, where outpatient surveillance with serial assessments of maternal and fetal well-being are undertaken. Furthermore, the incidence of severe hypertension was similar between the treated and untreated groups, highlighting that all women with hypertension in pregnancy require continued close surveillance to ensure that severe hypertension is recognised and managed appropriately. With regard to perinatal outcomes, FGR was more common among women with treated CH than other hypertensive groups, and similar to the rate observed among women with PE. These findings are consistent with other reports¹⁸, and likely reflect that women requiring treatment for CH have more severe disease. They are also more likely to have underlying conditions such as renal or connective tissue disease, themselves important contributors to placental insufficiency and FGR. Nevertheless, some of the observed differences may also be due to chance, given the small numbers and increased maternal age and smoking rates, in this group.

Although low-dose aspirin (initiated at or before 16 weeks gestation) has been found to reduce risk of PE^{19,20} and is widely recommended in international guidelines, many high-risk women in this cohort were not prescribed aspirin or calcium, despite the majority being seen initially prior to 16 weeks gestation. In particular, the prescription of aspirin in the CH groups was suboptimal, and the number of women who progressed to PE consistent with historical cohorts.¹⁸ The relative risk associated with aspirin administration and prevention of PE has been reported between 0.47¹⁹ and 0.76.²⁰ Based on this, an estimated 12¹⁹ to 19²⁰ cases of PE may have been averted in our cohort had this recommendation been followed, although this may overestimate the number of excess cases given that aspirin has greater efficacy in reducing the burden of early onset, compared to late onset, disease.²¹ Our study design was unable to answer the important question as to which women with risk factors may have received aspirin and subsequently did not develop pre-eclampsia.

To the best of our knowledge, prescribing patterns in pregnant women with hypertension in Australia have not been reported before. Although this was a single centre study, it was conducted at a large tertiary care hospital and data were collected over a 12-month period by a single researcher. The study relied solely on ICD coding for identification of cases. The small proportion of women who were prescribed medication limited our ability to conduct further analysis of that data.

In conclusion, while hypertension management guidelines were generally well followed, the opportunity for primary prevention of PE or FGR in high risk women with aspirin prophylaxis was frequently overlooked. Broader education beyond clinical practice guidelines of all maternity care providers is necessary to improve aspirin coverage in these women. In this cohort alone 12-19 excess PE cases may have been averted. Despite the findings of HYPITAT, uptake of the key trial recommendation to encourage delivery at or beyond 37 weeks in this cohort was low; however, we observed very low rates of adverse maternal outcome in women managed expectantly, suggesting that clinicians appropriately weigh up the likely maternal risk compared to infant benefits of deferred delivery in each case, a key recommendation of HYPITAT-II.

Acknowledgements

We would like to thank Denise van den Bosch for assistance with data entry and the Health Information Services team at the Mercy Hospital for Women for retrieving the medical

records. We acknowledge Andre Francis and Professor Jason Gardosi for help with the customised centiles.

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Guideline	Recommendation for initiation of treatment	Recommendation for antihypertensive medication	Use of low dose aspirin and/or calcium for the pre-eclampsia prevention	Timely delivery of pregnant women with hypertensive disorders
Society of Obstetric Medicine of Australia and New Zealand 2008³	Reasonable to initiate treatment at 140-160mmHg systolic and/or diastolic BP reaches 90-100mmHg on more than one occasion Severe hypertension defined as $\geq 170/ \geq 110$ mmHg	Methyldopa Labetalol Nifedipine Prazosin Oxprenolol Hydralazine	Low-dose aspirin is indicated for the secondary prevention of pre-eclampsia in women at increased risk Calcium should be offered to women at increased risk of developing pre-eclampsia, especially those with low dietary intake	Women who are at ≥ 37 gestational weeks should be considered for delivery, especially if the BP is not under control, the presence of a sign of severe pre-eclampsia or restricted fetal growth/ non-assuring fetal status.
Society of Obstetric Medicine of Australia and New Zealand 2014⁴	In the absence of compelling evidence, treatment of mild-moderate hypertension in the range of 140-160/90-100mmHg should be considered an option and will reflect local practice	Methyldopa Labetalol Nifedipine Prazosin Oxprenolol Hydralazine	Low-dose aspirin is indicated for women with at least moderate to high risk of pre-eclampsia i.e. secondary prevention of pre-eclampsia in women at increased risk and in women with significantly increased risk in their	Plan delivery in the best way on the best day in women who are at ≥ 37 gestational weeks

Severe hypertension defined as
 $\geq 160 / \geq 110 \text{ mmHg}$

first pregnancy
 Calcium should be offered to
 women with moderate to high risk
 of pre-eclampsia, especially those
 with low dietary intake

Table 1. SOMANZ guidelines for the management of hypertension during pregnancy

Table 2. Baseline maternal demographics and obstetric history (n = 516)

Characteristic	CH untreated (n=17)	CH treated (n=32)	GH untreated (n=239)	GH treated (n=29)	Pre- eclampsia (n=199)
Age (years) (mean $\pm$ SD)	31.82 $\pm$ 4.44	34.26 $\pm$ 5.61 ^{**, **1}	30.89 $\pm$ 5.22 ^{**}	32.64 $\pm$ 5.22	30.73 $\pm$ 5.32 ^{**1}
BMI (median [IQR])	32 (24-38) ^{*, *1, *2}	31 (25-37)	28 (24-34) [*]	27 (26-30) ^{*1}	27 (24-33) ^{*2}
Nulliparous [n (%)]	8 (47.1%)	15 (46.8%)	140 (58.6%)	22 (75.9%)	123 (61.8%)
Current smoker [n (%)]	1 (5.9%)	6 (18.8%)	20 (8.4%)	3 (10.3%)	22 (11.1%)

Existing indication for low-dose aspirin [n (%)] [∞]	17 (100%)	32(100%)	28 (11.7%)	0	37 (18.6%)
Prescribed low-dose aspirin [n (%)]	2 (11.8%) [†]	4 (12.5%) [†]	6 (21.4%) [‡]	0	9 (24.3%) [§]
Gestational week of initial visit (median [IQR])	11 (8-14)	10 (8-13)	15 (11-16)	0	12 (10-16)

[†] 1 woman was also prescribed calcium, [‡] 2 women were also prescribed calcium, [§] 4 women were also prescribed calcium,
[∞] based on the SOMANZ guideline for the management of hypertension in pregnancy 2008

^{*,*1,*2} p=0.03 ^{**,**1} p<0.01

^{1,2} groups which are being compared

Table 3. Thresholds for diagnosis of hypertension and initiation of anti-hypertensive treatment

	GH untreated (n=239)	GH treated (n=29)	CH treated (n=32; 15 initiated treatment during pregnancy)	Pre-eclampsia [n=199] 64 treated: GH (n=49), CH (n=15)
Systolic BP at the time of diagnosis (mean ± SD mmHg)	140 ± 10 mmHg	151 ± 13 mmHg	Pre-pregnancy	146±13 mmHg
Diastolic BP at the time of diagnosis (mean ± SD mmHg)	89 ± 8 mmHg	95 ± 9 mmHg	Pre-pregnancy	92 ± 9 mmHg
Gestational week at which the women were diagnosed with hypertension (mean ±SD)	35 ² weeks ± 31 days	32 ³ weeks ± 34 days	Pre-pregnancy	33 ¹ weeks ± 44 days
Systolic BP at which medication was initiated (median [IQR])	N/A	153 mmHg [140-156]	156 mmHg [135-215]	153 mmHg [130-185]
Diastolic BP at which medication was initiated (median [IQR])	N/A	94 mmHg (60-122)	97 mmHg (80-130)	99 mmHg (80-160)

Table 4. Neonatal outcomes (n=524)

Neonatal outcomes	CH untreated (n=17)	CH treated (n=32)	GH untreated (n=238)	GH treated (n=30)	Pre-eclampsia (n=207)
Gestational age at delivery weeks and days mean $\pm$ SD	38 ⁶ weeks $\pm$ 8 days**	37 ⁴ weeks $\pm$ 22 days***1	39 ³ weeks $\pm$ 13 days*** 1	38 ⁶ weeks $\pm$ 13 days**	36 ¹ weeks $\pm$ 29 days**
Customised birth weight centile mean $\pm$ SD (range) †	63.1 $\pm$ 28.5 (27.8-99.3)*	29.9 $\pm$ 23.5 (0.3-78.0)*	48.6 $\pm$ 31.1 (0.1-100.0)* ¹	43.6 $\pm$ 30.8 (0.4 – 95.4)	37.9 $\pm$ 32.1 (0.0-100)* ¹
Fetal growth restriction (FGR) n (%) †	0 (0%)	7 (21.9%)	30 (12.6%)	5 (16.7%)	45 (21.7%)
APGAR at 1 minute mean $\pm$ SD (range)	9 $\pm$ 1 (3-10)	7 $\pm$ 2 (0-9)	8 $\pm$ 2 (1-10)**	8 $\pm$ 2 (2-10)	7 $\pm$ 2 (0-10)**
APGAR at 5 minutes mean $\pm$ SD (range)	9 $\pm$ 1 (7-10)	9 $\pm$ 1 (6-10)	9 $\pm$ 1 (0-10)*	9 $\pm$ 1 (6-10)	9 $\pm$ 1 (0-10)*
NICU admission n (%)	1 (5.9%)	6 (18.8%)	12 (5.0%)	2 (6.7%)	59 (28.5%)
SCN admission n (%)	1 (5.9%)	0 (0%)	17 (7.1%)	3 (10.0%)	38 (18.4%)

†some missing data

*,*¹ p=0.02 **,**¹ p<0.01

^{1,2} groups which are being compared

Emergency LUCS: emergency caesarean

Elective LUCS: elective caesarean

IOL: induction of labour

SOL: spontaneous onset of labour

Figure 2. Mode of delivery per group

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Author/s:

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Title:

Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better?

Date:

2017-06-01

Citation:

Helou, A., Walker, S., Stewart, K. & George, J. (2017). Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better?. AUSTRALIAN & NEW ZEALAND JOURNAL OF OBSTETRICS & GYNAECOLOGY, 57 (3), pp.253-259. <https://doi.org/10.1111/ajo.12499>.

Persistent Link:

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