University of Cape Town

Faculty of Health Sciences

Hypoxaemia during tracheal intubation in patients with hypertensive disorders of pregnancy: analysis of data from an obstetric airway management registry

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Minor dissertation submitted in partial fulfilment of the requirements for the degree of Master of Medicine (MMed) in the
Department of Anaesthesia & Perioperative Medicine

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Declaration page

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Format

The contents of this minor dissertation are presented in the 'accepted for publication' format.

After establishment of the multicentre Obstetric Airway Management Registry (ObAMR) we initially performed a validation study of the first 200 records captured. Thereafter, we prospectively observed the following 202 cases comparing desaturation between hypertensive and non-hypertensive groups.

Both manuscripts have been accepted for publication and consist of the following:

1. Implementation and initial validation of a multicentre obstetric airway management registry (Published in *Southern African Journal of Anaesthesia and Analgesia* – Appendix 1).

   Please note, this article has not been registered for degree purposes and should not be used for examination. It is merely attached as an appendix for completeness.

2. Hypoxaemia during tracheal intubation in patients with hypertensive disorders of pregnancy: analysis of data from an obstetric airway management registry (Accepted for publication in the *International Journal of Obstetric Anesthesia*).

   This manuscript should be used for examination purposes.

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Contents

Declaration page....2
Format....3
Acknowledgements and contributions....4
Abstract....7
Chapter 1: Introduction....8
Chapter 2: Published paper....9
List of appendices....28
Appendix 1: Publication of initial validation study....29
Appendix 2: IJOA Letter of acceptance....35
Appendix 3: IJOA Reviewer comments....36
Appendix 4: IJOA Supplementary material....48
Appendix 5: IJOA Author guidelines....67
Appendix 6: Human Research Ethics Committee approvals....69
Appendix 7: NHRD registration....81
Appendix 8: Institutional approvals....84
Appendix 9: ObAMR theatre checklist....86
Appendix 10: ObAMR patient information poster....87
Appendix 11: STROBE checklist....88
Contact information....90

List of tables

Table 1: Classification of hypertensive disorders of pregnancy and patient characteristics

Table 2: The incidence of hypoxaemia (SpO_2 < 90%) in HDP and non-HDP patients

Table 3: Predictor variables of interest (n=402)

Table 4: Quantile regression models for 25th percentile of the SpO_2 nadir

List of figures

Figure 1: Box-and-whisker plot of SpO_2 nadir during airway management in patients with and without HDP.

Figure 2: Interaction plot of the combined effects of HDP and BMI on the 25th percentile (Q1) of SpO_2 nadir

List of appendices

Appendix 1: Publication of initial validation study

Appendix 2: IJOA Letter of acceptance

Appendix 3: IJOA Reviewer comments

Appendix 4: IJOA Supplementary material

Appendix 5: IJOA Author guidelines

Appendix 6: Human Research Ethics Committee approvals

Appendix 7: NHRD registration

Appendix 8: Institutional approval

Appendix 9: ObAMR theatre checklist

Appendix 10: ObAMR patient information poster

Appendix 11: STROBE checklist

Abstract

Background

In South Africa, hypertensive disorders of pregnancy are the leading cause of maternal mortality. More than 50% of anaesthesia-related deaths are attributed to complications of airway management. We compared the prevalence and risk factors for hypoxaemia (SpO_2<90%) during induction of general anaesthesia in parturients with and without hypertensive disorders of pregnancy. We hypothesised that hypertensive disorders of pregnancy are associated with desaturation during tracheal intubation.

Methods

Data from 402 cases in a multicentre obstetric airway management registry were analysed. The prevalence of peri-induction hypoxaemia (SpO_2<90%) was compared in patients with and without hypertensive disorders of pregnancy. Quantile regression of SpO_2 nadir was performed to identify confounding variables associated with, and mediators of hypoxaemia.

Results

In the cohort of 402 cases, hypoxaemia occurred in 19% with and 9% without hypertension (estimated risk difference, 10%; 95% CI 2% to 17%; *P*=0.005). Quantile regression demonstrated a lower SpO_2 nadir associated with hypertensive disorders of pregnancy as body mass index increased. Room-air oxygen saturation, Mallampati grade, and number of intubation attempts were associated with the relationship.

Conclusions

Clinically significant oxygen desaturation during airway management occurred twice as often in patients with hypertensive disorders of pregnancy, compounded by increasing body mass index. Intermediary factors in the pathway from hypertension to hypoxaemia were also identified.

Chapter 1: Introduction

The risk factors contributing to maternal mortality from general anaesthesia, especially in low-income and middle-income countries, and the burden of the problem have not been comprehensively studied up to now. Obstetric anaesthesia still accounts a large number of maternal deaths and exposure to general anaesthesia increases the odds of maternal and perinatal deaths.

The access to large datasets in obstetric anaesthesia is profoundly lacking. We implemented and established a multicentre Obstetric Airway Management Registry (ObAMR) in the Western Cape, South Africa, during 2018. This registry aims to enhance quality control, clinical governance, and monitor and assess airway management trends during general anaesthesia in this critically sensitive group of patients at obstetric facilities under supervision of the UCT Department of Anaesthesia and Perioperative Medicine.

The first 200 cases were recorded from September 2018 to January 2019. We performed an initial validation study on these records to confirm the accuracy of the online registry. Thereafter, we prospectively observed the following 202 cases and compared the desaturation experienced during induction of general anaesthesia between hypertensive and non-hypertensive groups.

We also aimed to obtain precise estimates of anaesthesia-attributed deaths in pregnant women exposed to general anaesthesia and to identify the factors linked to adverse outcomes in pregnant women.

Chapter 2: Published paper

The manuscript for the prospective observational study has been formatted for the International Journal of Obstetric Anesthesia. The letter of acceptance and reviewer comments can be found at the end of the minor dissertation under appendices. The 'Author Guidelines' for the journal can be found online at https://www.elsevier.com/journals/international-journal-of-obstetric-anesthesia/0959-289x/guide-for-authors or reproduced in the appendices.

Access to the publication can be found online at https://doi.org/10.1016/j.ijoa.2020.10.012.

Hypoxaemia during tracheal intubation in patients with hypertensive disorders of pregnancy: analysis of data from an obstetric airway management registry

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Background

In South Africa, hypertensive disorders of pregnancy are the leading cause of maternal mortality. More than 50% of anaesthesia-related deaths are attributed to complications of airway management. We compared the prevalence and risk factors for hypoxaemia (SpO_2<90%) during induction of general anaesthesia in parturients with and without hypertensive disorders of pregnancy. We hypothesised that hypertensive disorders of pregnancy are associated with desaturation during tracheal intubation.

Methods

Data from 402 cases in a multicentre obstetric airway management registry were analysed. The prevalence of peri-induction hypoxaemia (SpO_2<90%) was compared in patients with and without hypertensive disorders of pregnancy. Quantile regression of SpO_2 nadir was performed to identify confounding variables associated with, and mediators of hypoxaemia.

Results

In the cohort of 402 cases, hypoxaemia occurred in 19% with and 9% without hypertension (estimated risk difference, 10%; 95% CI 2% to 17%; *P*=0.005). Quantile regression demonstrated a lower SpO_2 nadir associated with hypertensive disorders of pregnancy as body mass index increased. Room-air oxygen saturation, Mallampati grade, and number of intubation attempts were associated with the relationship.

Conclusions

Clinically significant oxygen desaturation during airway management occurred twice as often in patients with hypertensive disorders of pregnancy, compounded by increasing body mass index. Intermediary factors in the pathway from hypertension to hypoxaemia were also identified.

Registry number: NHRD WC_201810_002

Keywords: Airway management; body mass index (BMI); gestational hypertension; hypertensive disorders; hypoxaemia; preeclampsia; pregnancy

Highlights

- Studied relationship between peri-induction hypoxaemia and hypertensive disorders of pregnancy.
- In the anaesthesia peri-induction period, 12% of patients had an SpO_2 nadir < 90%.
- Hypertensive patients were twice as likely to become hypoxaemic (19% vs 9%).
- Increasing body mass compounded the effect of hypertension on hypoxaemia.

Introduction

Post-caesarean mortality is 50 times higher in Africa than in high-income countries.[1] Anaesthesia-related maternal deaths are commonly associated with hypoxaemia and pulmonary aspiration.[1, 2] Furthermore, hypoxaemia is independently linked to poor maternal and fetal outcomes.[3] In South Africa, hypertensive disorders of pregnancy (HDP) are the leading overall cause of maternal death.[4] In the South African Saving Mothers Report, more than 50% of anaesthesia-related maternal mortality is attributed to complications of airway management.[4] General anaesthesia for caesarean section is commonly provided when there is a contraindication to neuraxial techniques (e.g. thrombocytopaenia in HDP), failed neuraxial anaesthesia, or extreme urgency.[5-8] Despite our understanding that HDP are associated with airway oedema and pulmonary oedema, the association between HDP and peri-induction hypoxaemia has never been studied. The value of establishing whether HDP are a predictor of hypoxaemia is particularly important in South Africa, where one in eight mothers suffer from preeclampsia or eclampsia.[1, 4]

The primary objective of this study was to compare the difference in incidence of clinically significant hypoxaemia (SpO_2<90%) during airway management in patients with and without HDP, requiring general anaesthesia from 20 weeks' gestation to 7 days postpartum. We hypothesised that HDP are associated with oxygen desaturation during airway management during induction of general anaesthesia. A secondary objective was to explore other anatomical and physiological risk factors associated with oxygen desaturation.

Methods

The Human Research Ethics Committee (HREC) of the Faculty of Health Sciences of the University of Cape Town (UCT) approved the establishment of the multicentre obstetric airway management registry (ObAMR) (UCT HREC Ref: 025/2018). All anaesthesia providers from the Department of Anaesthesia and Perioperative Medicine at UCT (including directly and indirectly supervised trainees, and consultant anaesthesiologists) were requested to prospectively capture data surrounding all obstetric general anaesthesia cases between 20 weeks' gestation and 7 days postpartum into the registry, beginning in September 2018. The overall rate of capture into the registry for all obstetric general anaesthesia cases was 80% in an earlier validation of the registry.[9] Patients undergoing both elective and emergency surgery are recruited from Groote Schuur, Mowbray Maternity and New Somerset Hospital in Cape Town, South Africa. Verbal consent for inclusion in the registry is sought from each patient. Records are collected anonymously in REDCap (Research Electronic Data Capture, https://www.project-redcap.org/) during or immediately after the case by using an electronic link sent to provider smartphones, or by scanning a QR code present in all obstetric theatres. The ObAMR is maintained on a secure password protected UCT server. Each electronic data capturing form is assigned a unique study number, with no personal identifying information. Therefore, later revalidation of data is not possible.

During interim analysis of the first 202 cases in the ObAMR, collected from 26 September 2018 to 11 January 2019, we observed a statistically significant difference in the proportion of peri-induction hypoxaemia (SpO_2<90%) in those with and without HDP (22% vs 7% respectively, *P*=0.002). At this time, we planned to use data from consecutive patients subsequently added to the registry, to confirm the result from the initial cohort of 202 cases and perform a formal analysis on the full cohort. The HREC of the Faculty of Health Sciences of UCT approved this study on data from the ObAMR (UCT HREC Ref: 342/2019). Data were prospectively collected for a further five months from 12 January 2019 to 27 May 2019.

Patients received routine obstetric management; for those with HDP, this includes fluid restriction, blood pressure management, and intravenous magnesium as seizure prophylaxis for disease with severe features. Standard practice for general anaesthesia for caesarean section taught at our centres includes preoxygenation using high-flow oxygen via a circle system and snug-fitting anaesthetic mask until an end-tidal oxygen fraction of at least 0.8 is achieved, followed by rapid sequence induction (RSI) and tracheal intubation with cricoid pressure.[10-14] In patients with HDP, the hypertensive response to tracheal intubation is obtunded by the use of bolus magnesium sulphate and/or a short-acting opioid. However, the exact general anaesthesia technique is at the discretion of the anaesthesiologist. Clinically significant hypoxaemia was dichotomously defined as presence or

absence of peripheral oxygen saturation < 90% during the tracheal intubation period starting from the time of intravenous induction of anaesthesia, to the $Sp0_2$ nadir observed prior to the maintenance phase of anaesthesia. The lowest manually observed SpO_2 value was recorded in the registry. For the purposes of this analysis, we defined HDP as patients who developed gestational hypertension, preeclampsia or eclampsia during their pregnancy. The diagnoses of HDP were made preoperatively by the obstetrician caring for the patient according to the current American College of Obstetricians and Gynaecologists guidelines.[15] Patients with pre-existing chronic hypertension that did not progress to preeclampsia were not categorised as having HDP.

We used the observed effect size from the first 202 cases to determine the sample size needed to test the hypothesis. The sample size for the primary outcome was based on the Z-test for independent proportions in the two groups; estimation was performed in G*Power (Heinrich Heine Universität, Düsseldorf, version 3.1.9.2). Given an expected ratio of 0.45 for patients with and without HDP and a risk of desaturation of 22% and 7% in respective groups (as per the first 202 cases), at a two-sided alpha value of 0.05, a further sample of 200 patients was required to detect a difference in proportions with >80% power. Simple descriptive statistics and frequency tables were used to summarise patient characteristics. The primary outcome was assessed by a Z-test for a difference in independent proportions of patients with hypoxaemia in the groups with and without HDP. We then performed a formal analysis on the combined 402 data set using the Bauer and Kohne[16] inverse chi-square test. This hypothesis test is used to account for the interim analysis and sample size re-estimation. An adjusted *P*-value for the combined analysis of the primary outcome is reported.

Quantile regression of SpO_2 nadir was performed to identify confounding variables associated with, and mediators of hypoxaemia. *A priori* specified confounders were body mass index (BMI), gestational age, the presence of active labour, and years of training of the anaesthesia provider. Mediators were airway oedema as assessed by the anaesthesiologist during laryngoscopy, baseline room-air SpO_2, Mallampati grade assessed immediately prior to anaesthesia, and the number of intubation attempts (defined as the number of times the laryngoscope blade was introduced). Years of training was categorised as less than one year, one to five years, and more than five years. In our setting, trainees are exposed to a high number of obstetric anaesthesia cases during their first year and gain significant experience in the management of these cases. Specialist anaesthesiologists have more than 5 years of training.

Due to the observation in the initial cohort that the presence of HDP specifically affects the lower end of the distribution of the SpO_2 nadir, the 25^{th} percentile was modelled by quantile regression analysis using the Barrodale-Roberts method. Independent and identically distributed random variables were assumed for estimation of the confidence intervals. Potential confounders associated with the SpO_2

nadir in univariable analysis were included in the multivariable model. Interaction between variables was tested in the final multivariable model. In mediation analysis, each mediator was individually tested in combination with HDP. Greater than 10% relative change in the estimated association between HDP and SpO_2 nadir was interpreted as a significant effect. To explore variation over time, we compared prevalence and association over consecutive epochs of 100 patients.

Data were extracted from the REDCap server to an Excel spreadsheet (Microsoft, Redmond, Washington, USA). Data analysis was performed in RStudio Team (RStudio: Integrated Development for R. RStudio, Inc., Boston, MA, 2016, http://www.rstudio.com/). In rare cases of missing data, the totals for the variable were adjusted accordingly. Recording of baseline (room air) oxygen saturation was only initiated with the second cohort.

The clean dataset for the study has been made available online through ZivaHub (https://doi.org/10.25375/uct.11854752). This study was reported according to the strengthening the reporting of observational studies in epidemiology (STROBE) statement.[17]

Results

We report on the first 402 patients captured in the ObAMR from September 2018 to May 2019. Cases were recorded from Groote Schuur (43.7%), Mowbray Maternity (36.1%) and New Somerset (20.3%) Hospitals. Tracheal intubation was performed by consultants in 6.5% of cases, supervised registrars and medical officers in 88.8%, and other junior doctors in 4.7%. Ten individual data points and one duplicate record were excluded when data points included typographical errors or were deemed physically impossible. Physiological outliers (unusual but plausible values) were not altered, as the data points could not be verified. Patients were categorised as HDP or non-HDP (Table 1). The prevalence of HDP in the complete cohort was 33% (134/402). Patient characteristics are displayed in Table 1, and indications for general anaesthesia are described in the Supplementary Table S1.

Table 1: Classification of hypertensive disorders of pregnancy and patient characteristics

Classification	**HDP (n = 134)**		**Non-HDP (n = 268)**	
Gestational hypertension	14 (3.5%)			
Preeclampsia	95 (23.6%)			
Chronic hypertension with superimposed preeclampsia	8 (2%)			
Eclampsia	17 (4.2%)			
Chronic hypertension			12 (3%)	
Normotensive			256 (63.7%)	
Characteristics	**n**	**Mean (SD) or median (IQR)**	**n**	**Mean (SD) or median (IQR)**
Age (years)	134	27.7 (7.0)	268	29.9 (6.3)
Weight (kg)	131	78.7 (20.8)	263	76.9 (19.9)
Height (cm)	132	161.0 (6.6)	264	162.6 (7.4)
BMI ($kg \cdot m^{-2}$)	131	30.4 (8.5)	263	29.0 (7.0)
Gestational age (weeks)	127	35.3 (4.0)	252	36.1 (4.7)
Parity	134	1 (0 – 2)	267	2 (1 – 3)
Gravidity	133	2 (1 – 3)	267	3 (2 – 4)

HDP: hypertensive disorders of pregnancy; BMI: body mass index; SD: standard deviation; IQR: interquartile range.

The primary outcome of hypoxaemia (SpO_2 < 90%) is presented in Table 2. In the first 202 cases, more patients with hypertensive disorders of pregnancy had peri-induction hypoxaemia (22% vs 7%, *P*=0.002). In the subsequent 200 patients, hypoxaemia occurred in 16% with- and 11% without hypertension (*P*=0.317), and in 19% and 9% in the combined cohort of 402 cases, with a risk difference of 10% (95%CI 2% to 17%, adjusted *P*=0.005).

The summary of variation in the data over time (grouped into epochs of 100 patients) is attached as Supplementary Figure S1. The distribution of predictor variables of interest is summarised in Table 3. The median (interquartile range [IQR]; range) SpO_2 nadir in those with HDP was 98 (92 - 99; 15 - 100) compared to 98 (96 - 99; 51 - 100) in those without (Figure 1). Twelve percent of all patients experienced SpO_2 below 90%.

Table 2: The incidence of hypoxaemia (SpO_2 < 90%) in HDP and non-HDP patients

	HDP	Non-HDP	Difference (95% CI)	P-value	Missing observations
First cohort (n = 202)	14/65 (22%)	9/135 (7%)	15% (4 to 26)	0.002	2
Second cohort (n = 199)[a]	11/67 (16%)	15/132 (11%)	5% (-5 to 15)	0.317	1
Entire cohort (n = 402)[a]	25/132 (19%)	24/267 (9%)	10% (2 to 17)	0.005[b]	3

[a]One duplicate record excluded. [b]Adjusted *P*-value for the *post-hoc* analysis of the combined dataset using the Bauer and Kohne inverse chi-square test. This test is based on the product of the two *P*-values and is judged against the critical value of a chi-square distribution with four degrees of freedom. HDP: hypertensive disorders of pregnancy; CI: confidence interval.

Table 3: Predictor variables of interest (n=402)

Continuous variables	**Mean**	**SD**
BMI ($kg \cdot m^{-2}$)	29.5	7.6
Gestational age (weeks)	35.8	4.5
Room air SpO_2 (%)	97.3	3.8
Categorical variables	**Frequency**	**Percentage (%)**
HDP	134	33.3
Active labour[a]	179	44.5
Mallampati score		
I	97	24.6
II	189	48.0
III	89	22.6
IV	19	4.8
Laryngoscopy attempts		
1	360	89.8
2	40	10.0
3	1	0.2
Oedema		
Absent	336	83.8
Mild	57	14.2
Severe	8	2.0
Years of training		
< 1	31	7.7
1-5	274	68.2
> 5	97	24.1

[a]First to third stages of labour. SD: standard deviation; BMI: body mass index; HDP: hypertensive disorders of pregnancy.

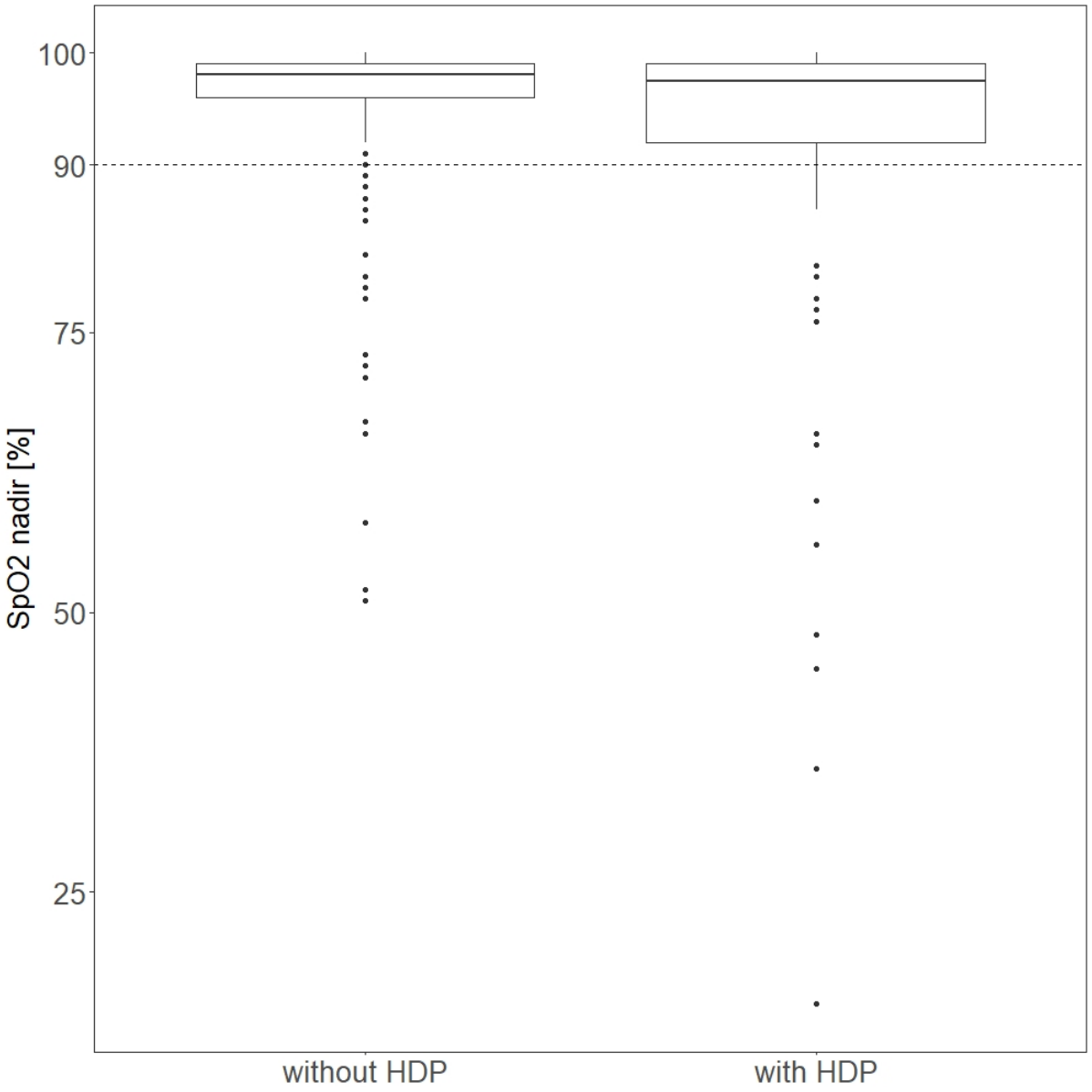

Figure 1. Box-and-whisker plot of SpO_2 nadir during airway management in patients with and without HDP. The clinically significant hypoxaemia threshold (SpO_2 90%) is indicated by the dashed line. HDP: hypertensive disorders of pregnancy. Boxes indicate median (bold line) with interquartile range. Whiskers indicate 1.5 x IQR above and below the first and third quartiles, with dots showing outliers.

Quantile regression analysis demonstrated that the presence of HDP is a predictor of the 25th percentile of SpO_2 nadir (Table 4 and Supplementary Table S2). HDP did not affect the 50th percentile (median) of SpO_2 (Supplementary Table S3 and S4). Of the potential confounding variables, BMI was significantly associated with SpO_2 nadir in the univariable analysis. The presence of active labour, gestational age, and number of training years were not associated with an SpO_2 nadir < 90%. The variables BMI and HDP were used in the multivariable and first order interaction models. The effects

of BMI and HDP were synergistic in the interaction model (Figure 2). Predicted values for the interaction model are presented in Supplementary Figure 5a to 5r. The estimates for HDP and BMI were not changed by the presence of active labour, gestational age and number of training years, and these variables were excluded from the final model. Airway oedema, number of attempts at tracheal intubation, Mallampati grade, and room air SpO_2 had a mediating effect on the relationship between HDP and SpO_2 nadir.

Table 4: Quantile regression models for 25th percentile of the SpO_2 nadir

Multivariable model: (HDP + BMI)	**Estimate[a]**	**95% CI**	***P*-value**	**Missing Observations**
HDP (reference: non-HDP)	-3.02	-4.05 to -1.98	<0.0001	11
BMI	-0.35	-0.41 to -0.28	<0.0001	
Interaction model: (HDP x BMI)				
HDP (reference: non-HDP)	11.36	7.84 to 14.88	<0.0001	11
BMI	-0.31	-0.38 to -0.24	<0.0001	
HDP: BMI	-0.54	-0.66 to -0.43	<0.0001	
Mediation analysis:				
HDP + RA SpO_2				
HDP (reference: non-HDP)	-2.00	-5.35 to 1.35	0.24	207[b]
SpO_2 (room air)	1.00	0.58 to 1.42	<0.0001	
HDP + Attempts				
HDP (reference: non-HDP)	-2.00	-4.66 to 0.66	0.14	3
Attempts (reference: 1)			<0.0001[c]	
Attempts 2	-24.00	-28.15 to -19.85	<0.0001	
Attempts 3	-58.00	-83.01 to -32.99	<0.0001	
HDP + Oedema				
HDP (reference: non-HDP)	-1.00	-3.85 to 1.85	0.49	3
Oedema (reference: absent)			<0.0001[c]	
Oedema: Mild	-7.00	-10.79 to -3.21	0.0003	
Oedema: Severe	-17.00	-26.09 to -7.91	0.0003	
HDP + Mallampati				
HDP (reference: non-HDP)	-1.00	-3.59 to 1.59	0.45	10
Mallampati (reference: I)			0.050[c]	
Mallampati II	0.00	-2.95 to 2.95	1.00	
Mallampati III	-1.00	-4.48 to 2.48	0.57	
Mallampati IV	-8.00	-13.96 to -2.04	0.01	

[a]Estimates are interpretable as unit change in saturation per unit change in risk factor; [b]Room-air SpO_2 was only added to the dataset after the first 202 cases were recorded; [c]*P*-value for the likelihood ratio test. HDP: hypertensive disorders of pregnancy; BMI: body mass index ($kg \cdot m^{-2}$).

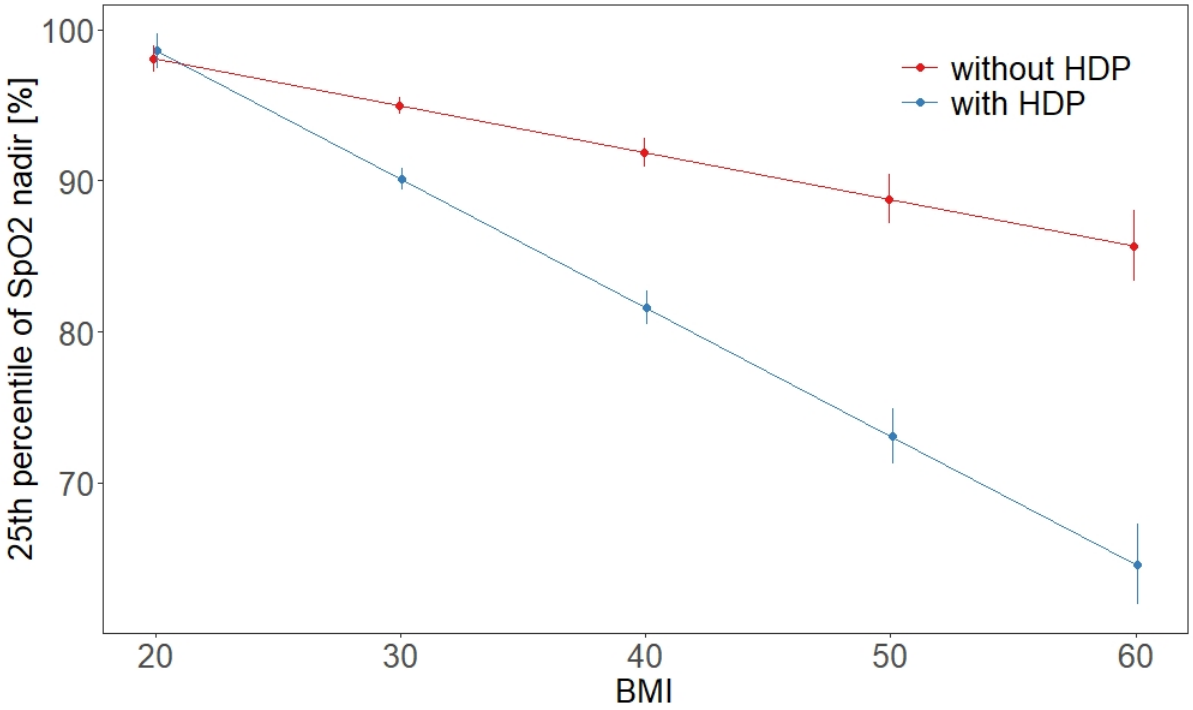

Figure 2. Interaction plot of the combined effects of HDP and BMI on the 25th percentile (Q1) of SpO_2 nadir. Vertical bars represent 95% confidence intervals. Blue and red lines represent predicted 25th percentiles for patient groups with and without HDP, respectively. HDP: hypertensive disorders of pregnancy; BMI: body mass index (kg m^{-2}).

Discussion

Significant hypoxaemia during obstetric airway management was a common event in our cohort; one in eight patients (12.3%) experienced an SpO_2 nadir < 90%, with a clinically significant difference in incidence between those with and without HDP. Close to one in five HDP patients (19%) experienced hypoxaemia, compared to one in ten (9%) in non-HDP patients. To our knowledge, this association between HDP and hypoxia during general anaesthesia has not been demonstrated previously in the literature. Another recent observational study in South Africa showed a similar overall prevalence of hypoxaemia during induction of general anaesthesia for caesarean section of approximately one in six patients (16.8%).[18]

Further exploration demonstrated that both HDP and BMI were associated with peri-induction hypoxaemia, and that the effects of these two risk factors were synergistic. In lean patients (BMI ≤20 kg m^{-2}), the 25th percentile for SpO_2 nadir was not significantly different between those with or without HDP, but as BMI increased, the nadir became progressively lower in those with HDP. Pragmatically, the combination of HDP and a BMI of greater than 30 kg·m^{-2} should alert the practitioner to a noteworthy risk of hypoxaemia during induction and airway management. It is important to note that the relationship between HDP and BMI is superadditive, and thus practitioners should be aware of the increased risks of this combination. Mediation analysis supports the hypothesis that low baseline room-air saturation, the presence of airway oedema, increasing Mallampati grade, and the number of attempts required for intubation, are partly responsible for the effect of HDP on saturation nadir.

Worldwide, HDP complicate 6–8% of all pregnancies,[19, 20] and preeclampsia is one of the leading causes of maternal morbidity and mortality.[21, 22] There are no studies focusing on hypoxaemia during and after tracheal intubation in women with HDP. In a recent study employing lung ultrasound, interstitial pulmonary oedema was found in 24% of preeclamptic women with severe features.[23] This is important, as interstitial oedema has been recognised as a ‘‘silent step” preceding alveolar oedema.[24] Even for patients without alveolar oedema, however, it is reasonable to hypothesise that the increased interstitial fluid may hamper gas exchange and reduce alveolar volume, thus decreasing functional residual capacity, leading to more rapid desaturation during apnoea. In addition, the presence of a raised left ventricular end-diastolic pressure (LVEDP),[23] particularly in patients with severe features of preeclampsia,[25] may predispose to pulmonary interstitial oedema during tracheal intubation, since LVEDP may rise acutely due to the hypertensive response. Although our study was not powered to assess this outcome, it is interesting to note that stratification by severity of HDP shows that hypoxaemia was more prevalent in patients with severe features of preeclampsia and/or eclampsia than patients with gestational hypertension or preeclampsia alone (33.3% versus 14.7% respectively).

Nonpregnant obese patients have a propensity to desaturate during induction of general anaesthesia, secondary to their reduced functional residual capacity and increased oxygen consumption.[26] In the recent study in South African women, BMI was shown to be an independent predictor of hypoxaemia.[18] A further observational study on the effects of administration of high flow humidified oxygen for preoxygenation in normotensive pregnant women showed a negative association between BMI and end-tidal oxygenation concentration.[27] This work is in keeping with the consistent relationship between BMI and desaturation in our data, and the synergy with the effect of HDP. Our study and those cited above[23, 25] therefore suggest that hypoxaemia in patients undergoing obstetric general anaesthesia is not simply the result of an *anatomically* more difficult airway but is compounded by the additional *physiological* changes due to HDP and increased BMI. Although high-flow nasal oxygenation has not been shown to be superior for preoxygenation in pregnant patients,[27] its role for apnoeic oxygenation remains to be studied. Our data suggest that if this strategy were to be successful, it would be most useful in patients with a combination of hypertensive disorders and obesity.

Our study has several limitations. We previously determined that 80% of all obstetric general anaesthesia cases are entered into the registry.[9] We believe it is unlikely that the presence or absence of airway challenges influenced reporting bias, but this has not been studied. Potential sources of the observed variation in ObAMR cohorts described here, include: i) biological variability (that is, true variability in the association between HDP and risk of desaturation), although such variability would not affect the overall conclusion; ii) changing airway management practice over time (for example, clinicians may have become alerted to the study hypothesis and may have been more careful to avoid desaturation); iii) variability in airway management between anaesthesia providers (different trainees and specialists rotating through the obstetric anaesthesia service), and iv) the reliability of data observation and entry. The overall incidence of hypoxaemia, however, was slightly higher in the second cohort than the first 202 patients, which would argue against increased vigilance or changing practice over time. Baseline (preoperative) saturation recordings were commenced with the second cohort in order to identify patients with pre-existing respiratory compromise.

Patient body mass captured in the registry may have been transcribed from the antepartum notes, as not all patients, particularly those presenting with maternal or fetal emergencies, were weighed immediately prior to delivery. Thus, the BMI values recorded may underestimate the true BMI, and the effect on hypoxaemia may thus also be underestimated. The grading of airway oedema is not validated, but the presence of mild or severe oedema was strongly associated with hypoxaemia.

The registry did not record the exact method of preoxygenation and patient positioning. In addition, recent obstetric Difficult Airway Society (DAS) guidelines suggest considering the use of low pressure

(<20 cmH_2O) mask ventilation with cricoid pressure during RSI,[12] which represents a departure from traditional teaching. Gentle mask ventilation and apnoeic oxygenation during RSI is, however, increasingly discussed in the literature and may occasionally have been practised in our cohort. Potential benefits would include the reduced likelihood of hypoxaemia and an early indication of whether face-mask ventilation is possible.[12] Additionally, a few patients experienced desaturation to below 70%, when pulse oximetry is no longer accurate. Nonetheless, the profound desaturation in several cases is noteworthy.

The principal finding of this prospective observational study was that clinically significant hypoxaemia during obstetric general anaesthesia occurred twice as often in patients with hypertensive disorders of pregnancy as in those without. In addition to HDP, BMI was an important predictor of SpO_2 nadir. Further work is required to assess the role of mediators identified in this study. Airway oedema may lead to anatomical difficulty and multiple intubation attempts. Low room air oxygen saturation prior to airway management should be considered as a marker of physiological compromise. Future prospective studies of the ongoing registry dataset, or other prospective studies with planned causal analysis should elucidate the value of preventative strategies, such as the administration of gentle mask ventilation or high-flow nasal oxygen in order to prolong apnoeic oxygenation, particularly in patients with HDP.

Authors' contributions:

Study conception: M.I.S., R.A.D., R.H.

Study design: M.I.S., L.D.T., R.H.

Writing and submission of protocol and document for HREC assessment: M.I.S., L.D.T., R.H.

Drafting, revising, and completing the trial registration: R.H.

Data acquisition: M.I.S., D.V.D., A.R., R.H.

Data analysis: L.D.T., C.L.

Data interpretation: L.D.T., C.L.

Drafting of manuscript: M.I.S., L.D.T., R.A.D., R.H.

Revising of manuscript: all authors.

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Declaration of interests

The authors declare that they have no conflicts of interest.

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List of appendices

Appendix 1: Publication of initial validation study

Appendix 2: IJOA Letter of acceptance

Appendix 3: IJOA Reviewer comments

Appendix 4: IJOA Supplementary material

Appendix 5: IJOA Author guidelines

Appendix 6: Human Research Ethics Committee approvals

Appendix 7: NHRD registration

Appendix 8: Institutional approval

Appendix 9: ObAMR theatre checklist

Appendix 10: ObAMR patient information poster

Appendix 11: STROBE checklist

Appendix 1: Publication of initial validation study

The initial validation study has been published in the *Southern African Journal of Anaesthesia and Analgesia*.

Access to the publication can be found online at https://doi.org/10.36303/SAJAA.2020.26.4.2423.

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ORIGINAL RESEARCH

Implementation and initial validation of a multicentre obstetric airway management registry

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Background: In Africa, maternal mortality after caesarean delivery is 50 times greater than in high-income countries. In South Africa, more than 50% of anaesthesia-related maternal mortality is attributed to failure to protect the airway. We implemented an obstetric airway management registry, to facilitate future improvements in management and outcomes.
Methods: A prospective electronic registry was established at three obstetric sites in Cape Town, recording airway management for all general anaesthetics from 20 weeks gestation to seven days post-partum. Perioperative descriptive data are entered using a web-based smartphone-enabled platform. To quantify the reliability of capture, we compared the first 200 records in the registry to theatre logbooks. We used summary statistics to describe our obstetric anaesthesia population, and details relevant to airway management.
Results: The first 200 cases were recorded from September 2018 to January 2019. According to theatre logbooks, this represented 80% of cases performed. Major indications for general anaesthesia included severe fetal distress/bradycardia (21%), failed neuraxial technique (19%), coagulopathy (19%), and abnormal placentation (12%). A third of patients had hypertensive disorders of pregnancy, and 6% had imminent/confirmed eclampsia. Forty per cent were in active labour. On airway assessment, Mallampati grade was 3 or 4 in 29% of patients, and mouth opening, thyromental distance and mandibular protrusion limited in 10%, 8% and 8% respectively. Cormack-Lehane grade IIb and III views were encountered in 6% and 2% respectively, with no grade IV views. Desaturation below 90% occurred in 12% of patients. There were two cases (1%) of failed intubation with supraglottic airway rescue, and no emergency surgical airways performed.
Conclusion: An obstetric airway management registry was successfully implemented. Clinically significant hypoxaemia occurred commonly during general anaesthesia, with a high incidence of difficult intubation predictors and desaturation. The registry will guide research aimed at improving safety during general anaesthesia in obstetrics.

Keywords: airway management, general anaesthesia, hypoxaemia, obstetric anaesthesia, pregnancy, registry
Registry number: NHRD WC_201810_002

Introduction

The African Surgical Outcomes Study showed that maternal mortality after caesarean delivery is 50 times greater in Africa, predominantly from obstetric haemorrhage and anaesthesia-related hypoxaemia or pulmonary aspiration.[1,2] The South African Saving Mothers Report (2014–2016) showed that 61/87 (70%) of anaesthesia-related deaths were attributed to complications of airway management.[3] Lack of skilled doctors was recorded in 71% of these deaths, and a quarter of all anaesthetics were administered by non-physician anaesthesia providers.[3]

Obstetric airway management features increased difficulty and complications.[4] Anatomical and physiological changes that occur during pregnancy increase the likelihood of difficult or failed intubation,[5] which may be up to eight times higher than in the general surgical population.[6-9] Maternal deaths from difficult airway management have been highlighted in two reports of the Confidential Enquiries into Maternal Deaths in the United Kingdom (2006–2008 and 2000–2002).[10,11] The American Society of Anaesthesiologists' Closed Claims in obstetrics database revealed that maternal deaths were more frequently associated with general than regional anaesthesia, and that 16% of the anaesthetic claims were due to critical events involving the airway and respiratory system.[12]

We sought to describe the clinical characteristics, contributors to, and outcomes of obstetric airway management within our context, and to test an online data collection tool. We aimed to quantify the reliability of captured cases; hence, the primary outcome of this validation study was to establish the proportion of the total number of general anaesthetics (GAs) performed, which were captured in the registry. We therefore compared the first 200 patients in the registry with the number of theatre logbook entries for the corresponding period. The secondary outcome was a detailed description of our obstetric anaesthesia population requiring GA, including predictors of difficult airway management, and outcomes. The aim of this ongoing registry is to address the lack of data in our context, identify trends, and provide the basis for future quality improvement projects in airway management.

Method

A multicentre Obstetric Airway Management Registry (ObAMR) was established after approval by the Human Research Ethics Committee (HREC) of the Health Sciences Faculty of the University of Cape Town (UCT) (HREC Ref: R025/2018). The ongoing registry was approved for a duration of three years from 26 September 2018 to 30 September 2021. Perioperative data describing patient demographics, indications for GA, factors predictive of a

difficult airway, airway management techniques, complications and outcomes are collected at Groote Schuur (GSH), Mowbray Maternity (MMH) and New Somerset (NSH) Hospitals under the clinical supervision of the Department of Anaesthesia and Perioperative Medicine of UCT.

All patients requiring GA after 20 weeks gestation and up to seven days post-delivery are included. Simple verbal consent for inclusion in the registry was approved by HREC. Preoxygenation to an end-tidal oxygen fraction > 0.8, followed by rapid sequence induction (RSI) and tracheal intubation with cricoid pressure is taught as standard practice at our centres.[4,13-16] However, the GA technique provided is ultimately at the discretion of the anaesthesiologist. All anaesthesia providers from the Department of Anaesthesia and Perioperative Medicine of UCT can enter data into the registry. Records are collected anonymously on REDCap (Research Electronic Data Capture, https://www.project-redcap.org/) during or immediately after the case by using an electronic link sent to their smartphones (www.tinyurl.com/ObAMR), or by scanning a QR code present in all obstetric theatres. The ObAMR is maintained on a secure password protected UCT server. Each electronic data capturing form is assigned a unique study number, with no personal identifying information.

The HREC of the Health Sciences Faculty of UCT approved the validation and initial description of the first 200 cases entered into the ObAMR (UCT HREC Ref: 341/2019). Data were collected from 26 September 2018 to 9 January 2019. Data were extracted from the REDCap server to an Excel spreadsheet (Microsoft, Redmond, Washington, USA). The primary outcome was assessed by establishing the proportion of general anaesthetics captured, by comparing the number of records in the registry and the total number of cases entered in the operating theatre logbooks over the same time period. For secondary outcomes, baseline patient characteristics were reported as mean (standard deviation [SD]) for continuous normally distributed variables, median (interquartile range [IQR]) for data not normally distributed, and number (percentage) for categorical variables. In addition, details relating to airway management were reported, including experience of anaesthesia provider, airway assessment, laryngoscopic view, and outcomes such as incidence of failed intubation and rescue, and nadir of oxygen saturation (< 90% defined as clinically significant). The detailed data capture sheet is available as Supplementary Material, Appendix 1.

Results

Cases were recorded at GSH (tertiary academic, 40%), MMH (regional obstetric, 39%) and NSH (regional, 21%). When compared to theatre logbooks, overall 80% of GAs were captured in the ObAMR (Table I). The obstetric GA rate at these centres was approximately 11% of all caesarean sections performed. At MMH there was a failure to record conversions from regional to general anaesthesia in the theatre logbooks, with one more GA case entered in the registry than recorded in theatre. This led to a falsely elevated capture rate of 101% at this institution. We excluded 32 patients requiring GA for infertility procedures (< 20 weeks gestation) at GSH, that had been entered in the theatre logbooks. Two incomplete records in the registry, with no location specified, were also excluded.

Table I: Validation data and location

	GSH	MMH	NSH	Total
Theatre logbooks	105*	76	66	247
ObAMR	80	77	41	198†
Capture rate	**76%**	**101%**	**62%**	**80%**

GSH – Groote Schuur Hospital, MMH – Mowbray Maternity Hospital, NSH – New Somerset Hospital, ObAMR – Obstetric Airway Management Registry
*32 ultrasound-guided oocyte retrievals at GSH were excluded (< 20 weeks gestation)
†2 incomplete records excluded; locations not specified

Patient demographic details are presented in Table II. Mean (SD) age was 29.5 (6.4) years, weight 77.2 (19.6) kg and body mass index (BMI) 29.3 (7.5) kg/m^2. Median (IQR) gestational age was 37 (33–39) weeks. Major indications for general anaesthesia included severe fetal distress/bradycardia in 21%, failed neuraxial technique in 19%, suspected or confirmed coagulopathy in 19%, and the presence of abnormal placentation (e.g. abruptio placentae/placenta praevia/accreta) in 12% of cases. Neuraxial anaesthesia was the primary anaesthetic strategy in 24% of cases who subsequently underwent GA. Hypertensive disorders of pregnancy were present in 33%, with 6% developing imminent or confirmed eclampsia. Forty per cent of patients were in active labour.

Table II: Patient demographic details

	Minimum	Maximum	Mean/ median	SD/IQR	*n*
Age (years)	15	44	29.5	6.4	200
Height (cm)	145	180	162.5	6.6	197
Weight (kg)	39	170	77.3	19.6	197
BMI (kg/m^2)	17.3	72.6	29.3	7.5	197
Gestation (weeks)	20	42	37	33–39	190
Parity	0	8	1	0–2	199
Gravidity	1	8	2	1–4	199

BMI – body mass index, SD – standard deviation, IQR – interquartile range

In this analysis, 89% of anaesthesia providers were medical officers and/or anaesthesia registrars with more than one year of experience of clinical anaesthesia. On airway assessment, Mallampati grade 3 or 4 was present in 29% of cases, and mouth opening, thyromental distance and mandibular protrusion were limited in 10%, 8% and 8% respectively (Table III).

Rapid sequence induction with an endotracheal tube (ETT) was the primary strategy in 72%. Suxamethonium was the muscle relaxant used in 97% of cases. First-pass intubation success was 87%, and an introducer was used in 21%. Traditional Macintosh laryngoscope blades were used in 73% of intubations. Videolaryngoscopes were available in 98%, but only used in 26% of intubations. Cormack-Lehane grade IIb and III laryngoscopic

views were encountered in 6% and 2% respectively, with no grade IV views.

Mild or severe airway oedema was encountered in 17%, as assessed clinically during laryngoscopy. Range (median; IQR) of saturation nadir was 15 to 100% (98; 95–99), with 12% of patients below 90%. Desaturation was more common in patients with pregnancy-related hypertension (22% versus 7%, $p = 0.0021$). There were two cases (1%) of failed intubation with supraglottic airway rescue, no emergency front of neck surgical access was required, and there were no deaths.

Table III: Airway assessment and management

Provider demographic details:	Frequency	Percentage (%)	*n*
Level of qualification			
Intern	4	2	
Community service doctor	7	3.5	
Medical officer	66	33	200
Registrar	111	55.5	
Consultant	12	6	
Years of experience			
< 1 year	21	10.5	
1–5 years	130	65	200
> 5 years	49	24.5	
Airway assessment:			
Mallampati			
I	44	22	
II	95	47.5	
III	48	24	200
IV	9	4.5	
Not assessed	4	2	
Dentition			
Full	155	77.5	
Partial present	36	18	200
Partial absent	7	3.5	
Edentulous	2	1	
Thyromental distance			
≥ 6.5 cm or 4 fingers	150	75.4	
< 6.5 cm or 4 fingers	15	7.5	199
Not assessed	34	17.1	
Inter-incisor gap			
≥ 5 cm or 3 fingers	170	85	
< 5 cm or 3 fingers	19	9.5	200
Not assessed	11	5.5	
Neck mobility			
≥ 35 degrees	171	85.5	
< 35 degrees	1	0.5	200
Not assessed	28	14	
Mandibular protrusion			
Class A	89	44.7	
Class B	12	6	199
Class C	3	1.5	
Not assessed	95	47.7	
Airway management:			
Primary strategy			
GA + ETT	144	72	
GA + SGA	4	2	200
Neuraxial	48	24	
Other	4	2	
Muscle relaxant			
None	4	2	
Suxamethonium	194	97	
Rocuronium	2	1	200
Cisatracurium	-	-	
Other	-	-	
Laryngoscope blade			
Macintosh 3	122	61.3	
Macintosh 4	24	12.1	
CMAC 3	27	13.6	199
CMAC 4	19	9.5	
CMAC D	4	2	
None	3	1.5	
Direct C-L view			
Grade I	155	77.5	
Grade IIa	25	12.5	
Grade IIb	12	6	200
Grade III	4	2	
Grade IV	-	-	
Not assessed	4	2	
Airway oedema			
Absent	167	83.5	
Mild	28	14	200
Severe	5	2.5	
Intubation attempts			
1	174	87	
2	25	12.5	200
3	1	0.5	
4	-	-	
Introducer			
Yes	41	20.5	200
No	159	79.5	
Videolaryngoscope used			
Yes	56	28	200
No	144	72	
Supraglottic device used			
Yes	2	1	200
No	198	99	
Front of neck access			
Yes	-	-	200
No	200	100	
SpO_2 nadir			
< 90%	23	11.5	200
> 90%	177	88.5	

GA – general anaesthesia, ETT – endotracheal tube, SGA – supraglottic airway, C-L – Cormack-Lehane

Discussion

The primary outcome of this analysis showed that 80% of obstetric GA cases performed during September 2018 and January 2019 at GSH, MMH and NSH were captured in the ObAMR by means of an online data-capturing tool. This begins to address the scarcity of airway-specific registry data for obstetric GA in the literature.

On airway assessment, we encountered a high prevalence of factors predicting difficult tracheal intubation. Clinically significant hypoxaemia (saturation nadir < 90%) occurred in approximately one in eight patients (12%) and was more common in patients with hypertensive disorders of pregnancy. The overall incidence of hypoxaemia is similar to that described in a recent observational study conducted elsewhere in South Africa (16.8%).[17]

Neuraxial anaesthesia offers advantages in obstetric patients in terms of avoidance of airway management.[18] Over the past 20 years, there has been a significant reduction in the use of GA for caesarean section, with corresponding increased use of neuraxial techniques.[19] The challenges surrounding safe and timely securing of the airway in the obstetric patient are a major cause of morbidity and mortality in any setting.[19] In 38 (19%) patients in our study, the primary indication for GA was failed neuraxial anaesthesia. This highlights an area for quality improvement in our setting.

Airway difficulty has been reported to be eight times more common in obstetric patients compared to the general surgical population,[7] with the incidence of difficult or failed tracheal intubation remaining at 2.6 (95% CI 2.0–3.2) per 1 000 anaesthetics (1 in 390) for obstetric general anaesthesia.[7] Maternal mortality from failed intubation is 2.3 (95% CI 0.3–8.2) per 100 000 of all GAs for caesarean section (one death per 90 failed intubations),[7] and occurs from hypoxaemia secondary to airway obstruction or oesophageal intubation, or pulmonary aspiration.[4,7] In this analysis, there were two cases of failed intubation (1%) with successful supraglottic airway rescue, and no emergency front of neck surgical access was required. There were no maternal deaths recorded in the registry.

Most airway catastrophes occur when airway difficulty is not anticipated prior to induction of anaesthesia.[5] Timely evaluation of the parturient's airway and adequate preparation to deal with potential complications are helpful in avoiding airway disasters. There are a few simple preoperative bedside clinical tests that can be performed to evaluate the airway, including the Mallampati score, mouth opening (inter-incisor gap), thyromental distance, neck mobility (atlanto-occipital extension), and ability to protrude the mandible.[5,20,21] The relationship between increased grades of airway classification and relative difficulty of intubation in parturients undergoing caesarean delivery during GA, has been studied by Rocke et al.[22] They found that the relative risk of difficult intubation in a parturient with a Mallampati class 3 airway was 7.58 times higher than in a parturient with a class 1 airway. This relative risk increased to 11.3 in patients with a class 4 airway.[22] We encountered Mallampati grade 3 or 4 in 29% of cases, and mouth opening, thyromental distance and mandibular protrusion were often limited.

Maternal, fetal, surgical and situational factors contribute to the increased incidence of failed intubation. Many physiological changes occur during pregnancy, including physical characteristics such as increased BMI, breast enlargement, and generalised oedema. The mucosa of the upper respiratory tract also becomes more vascular and oedematous, especially during labour,[23] leading to increased risk of airway bleeding and swelling.[20] Fluid retention in head and neck tissues during pregnancy potentially narrows the upper airway and reduces compliance, making laryngoscopy more difficult.[19] Clinical teaching is that pharyngeal oedema may be exacerbated by preeclampsia and eclampsia, although there is limited literature to support this statement. In this analysis mild or severe airway oedema was encountered in 17% of patients. Videolaryngoscopy (VL) has been suggested as a useful adjunct for both anticipated and unanticipated difficulty in obstetric GA. The low rates of usage of VL and tracheal tube introducers in our registry (despite near-ubiquitous availability) is cause for concern, and an obvious target for quality improvement.

There were several limitations of our study. The overall rate of capture of approximately 80% into the registry reflects that at least 20% of general anaesthesia cases were omitted. However, if the elevation of the capture rate due to the documentation practice at MMH is excluded, the rate may have been only 71%. It is unlikely that any category of airway challenge would have had a higher likelihood of reporting or omission, so that selection bias probably did not influence the outcome. Although the registry is rapidly completed by the attending anaesthetist, it is possible that periods of high case load may have reduced reporting. The ethical considerations concerning anonymity precluded our establishing the clinical circumstances of the cases not captured. Every attempt will be made to increase the capture rate, by emphasising the long-term benefits to patient safety of maintaining a complete registry. The anaesthesia provider during the GA was responsible for capturing the data onto the ObAMR, and data entry errors may have occurred. The online data capturing tool included definitions and pictures as a guideline, but certain data fields including preoperative airway assessment are subject to inter-observer variability. As clinicians were ultimately responsible for the GA technique, there may have been non-standardised performance. It was therefore often difficult to identify the contributing factors for the high incidence of hypoxaemia in our study.

Strengths of our study include the successful establishment of the ObAMR, which we believe to be the first online database collecting information on airway management in the pregnant population in our setting. The aims of this registry are to enhance quality control and clinical governance, and to monitor and assess airway management trends during GA in this high-risk group of patients.

The results of this initial analysis show that our online data-capturing tool is valuable for collecting information on airway management in the obstetric population. Hypoxaemia during GA for obstetric patients is still common. This registry will allow for broader analysis to be conducted on larger datasets and serve as the basis for the performance of future interventional studies.

Acknowledgements

The authors would like to thank their colleagues in the Department of Anaesthesia and Perioperative Medicine of the University of Cape Town for collecting ObAMR data, and our patients for consenting to participate and expand medical knowledge.

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding source

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Ethics approval

A multicentre Obstetric Airway Management Registry (ObAMR) was established after approval by the Human Research Ethics Committee (HREC) of the Health Sciences Faculty of the University of Cape Town (UCT) (HREC Ref: R025/2018).

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Appendix 1 on next page

Appendix 2: IJOA Letter of acceptance

Gmail **Maretha Smit <marethas.smit@gmail.com>**

Decision on submission to International Journal of Obstetric Anesthesia

1 message

International Journal of Obstetric Anesthesia <em@editorialmanager.com> Sat, Oct 24, 2020 at 8:40 AM
Reply-To: International Journal of Obstetric Anesthesia <ijoa@elsevier.com>
To: Maretha Isabel Smit <maretha.smit@uct.ac.za>

CC: cynthia-wong@uiowa.edu

Manuscript Number: YIJOA-D-20-00209R3

Hypoxaemia during tracheal intubation in patients with hypertensive disorders of pregnancy: analysis of data from an obstetric airway management registry

Dear Dr. Smit,

Thank you for re-submitting your manuscript to International Journal of Obstetric Anesthesia.

I am pleased to inform you that your revised submission has now been accepted for publication, after editing in journal style and some minor word changes.

Your accepted manuscript will now be transferred to our production department. We will create a proof which you will be asked to check, and you will also be asked to complete a number of online forms required for publication. If we need additional information from you during the production process, we will contact you directly.

We appreciate you submitting your manuscript to International Journal of Obstetric Anesthesia and hope you will consider us again for future submissions.

Kind regards,
Michael Paech
Editor-in-Chief

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Appendix 3: IJOA Reviewer comments

Response to review – IJOA manuscript YIJOA-D-20-00209

If you elect to submit a revised manuscript, I would appreciate your noting all changes in the manuscript by using red font. This helps the reviewers assess your responses to their comments.

Noted, thank you. We have indicated all changes in this fashion.

I would also appreciate your review of the Journal's reference format (see the Guide for Authors), and revision of the reference list to comply with this format.

We have checked and updated as appropriate.

Reviewer #1:

An observational study of hypoxia during induction of general anaesthesia in pregnant women is presented. The authors have analysed their database comparing women with and without hypertensive disease of pregnancy (HDP). Women with hypertension were more likely to desaturate below 90% than those without. The manuscript is well written and easy to follow as would be expected from a unit with an international reputation for high-quality research.

Thank you.

1. It would appear that the authors created a database for obstetric general anaesthesia and after looking at the first 200 cases generated a hypothesis that desaturation (defined as an SpO2 <90%) was more common in women with HDP. Only at this point do they appear to have set up the study to compare outcomes between those with and without HDP. It could be argued that this is not the ideal way to perform scientific research with hypothesis generation after initial data analysis.

The primary purpose of gathering data in a registry is to improve quality assurance and clinical outcomes. Having observed an unexpected association, we then structured further prospective analysis of the data to confirm this observation. We have accounted for this study design in detail in the primary analysis.

2. Rather than comparing women with and without HDP, did the authors consider looking at all episodes of maternal hypoxia and investigate which factors made this outcome more likely to develop? Presumably HDP would have been one of a number of risk factors. Statistical analysis would identify which variables were most important.

> In this analysis we focused on the role of HDP in hypoxaemia. Other analyses of physiological and anatomical airway factors are under way.

3. The study compares general anaesthesia in women with and without HDP. The control group is therefore any women who received a general anaesthetic and did not have HDP. Did the authors consider a case-control structure to their methodology in which greater effort was made to compare women of similar demographics?

> In an analysis of such registry data, it was not thought appropriate, and indeed not feasible, to use the case control design. We therefore adjusted for demographic variables in our analysis. Table 2 shows good comparability between the two groups, with the demographic profiles of the two groups very closely matching to the overall profile of the registry. Thus, we feel that we have an unbiased estimate of the HDP effect.

4. It is well recognised that airway management is more challenging in pregnant women and made more complex in those with HDP. The upper airway in HDP is narrowed (Izci et al. Am J Resp Crit Care Med 2003; 167: 137-40) and interstitial lung fluid is increased with greater severity of disease (Zieleskiewicz et al Anesthesiology 2014; 120: 906-14). These studies (and others) explain both the anatomical and physiological mechanisms the authors wished to investigate. Furthermore, it is also accepted that hypoxia develops more quickly in the obese and desaturation is more likely with multiple attempts at intubation. Consequently, the findings of this study are not unexpected.

> We concur with the reviewer that explanatory mechanisms which suggest that hypoxaemia may occur, have been described in the literature. However, hypoxaemia during tracheal intubation in patients with HDP is of critical clinical importance and has neither been specifically studied nor demonstrated in the literature. We believe our study fills this gap, linking the anatomical and physiological mechanisms and demonstrating the clinical occurrence of hypoxaemia. We emphasize this in the first paragraph of the discussion.

5. HDP is not a heterogeneous condition and severe early-onset disease is quite different to the milder form of the disease at term. Did the authors make an attempt to look at the severity of the condition and do they consider this to be an important issue when interpreting their findings? Furthermore, there is no information on treatment of HDP in the preoperative period, most notably in terms of drug and fluid management. Presumably this would be different in the two populations under investigation.

> Though not powered to distinguish between patients with different levels of severity of disease, we do report in the Discussion, paragraph 3, that desaturation occurred twice as frequently in patients with severe disease (33 vs 15%). We have made a comment to emphasise the lack of statistical power in this regard, in the Discussion. With respect to the comment about differences in management, we have added a comment as to the routine management of patients with HDP in our unit, in the Methods section, paragraph 3.

6. The authors highlight the lack of anaesthetic data when discussing the limitations of the study. This is a significant issue as the reader is unaware how patients were anaesthetised and whether differences in technique between the two groups could affect outcome. General anaesthetic techniques differ markedly when comparing those with and without HDP, most obviously in the use of agents to attenuate the stress

response to laryngoscopy and intubation. Furthermore (and highlighted by the authors) anaesthetic technique may have changed during the course of the study when practitioners became aware of specific data collection.

The standard practice of general anaesthesia for patients with and without HDP in our unit is described in the Methods section. Although it is possible that anaesthesia technique could have changed over time, this seems an unlikely explanation of the observed association, as there was no reduction in the overall incidence of hypoxaemia in time, as noted in the limitations and demonstrated in our breakdown of the data into epochs of 100 cases (Supplementary Figure S1).

7. The technique of pre-oxygenation does not appear to have been standardised. Can the authors be sure that in all cases pre-oxygenation was with high-flow oxygen (>10 L/min) via a tight fitting mask for a specified duration? Was high-flow nasal oxygen (HFNO) used in any of the cases? Was end-tidal oxygen >90% achieved in all cases?

The standard practice in our institution is preoxygenation using a tight-fitting mask until an end-tidal concentration of 0.8 is reached. This has been added in the Methods section, paragraph 3.

8. There are no data on the indications for caesarean section. We are told that both elective and emergency cases were included. Were there more urgent and emergency procedures in the HDP group? If so, could this affect outcome?

We have added a description of the indications for CS to the Supplementary file (Table S1). We feel that it is unlikely that this affected outcome, and it reflects normal clinical practice.

9. Why did the authors choose 90% as their cut off for hypoxaemia? Oxygen saturations are a continuous variable and to pick an arbitrary level needs to be justified. Of note, another recent study on pre-oxygenation and HFNO used 93% as the cut off (Lodenius et al Anaesthesia 2018; 73: 564).

We feel that since 90% is globally accepted as the inflection point of the oxyhaemoglobin saturation curve, whereafter desaturation is rapid, this was the clinically most relevant level for our study. This decision was made prior to data analysis.

10. The text and Figure 1 suggest extremely low oxygen saturations (<70%) were recorded in a small number of women. How accurate are pulse oximeters at such low values?

It is accepted that the accuracy of pulse oximeters decays at values below 75%. Dichotomisation of patients into hypoxaemic and non-hypoxaemic using a threshold of 90% helps to improve accuracy of the analysis. In Figure 1, patients with saturations below 70% are clearly marked as outliers. Although unlikely to affect the outcome, we have added a statement to this effect in the limitations (Discussion, paragraph 7).

11. The authors highlight that BMI data may be inaccurate as values from early pregnancy may have been used. Given the importance of BMI in this study, the potential inaccuracy cannot be ignored and this limitation minimises the impact of the study's findings. Also it is unclear when the Mallampati score was assessed. It is well known that Mallampati scores change during pregnancy and during labour.

Since the BMIs may have based upon early pregnancy body mass, true BMIs may have been underestimated. This is stated in the limitations. However, since BMI increases during pregnancy, the effect that we describe is in fact also an underestimate. This comment has been added to the Discussion of limitations where it was originally present in the text.

With respect to the time at which the Mallampati score was assessed, we have added the phrase “assessed immediately prior to anaesthesia” to the Methods section, Page 5, paragraph 2. We have also included the CRF of the registry in the Supplementary file.

12. The absence of baseline SpO2 levels (RA SpO2) in over half the patients is another weakness of the study which should be included in the discussion of the study's limitations.

A comment has been added on Page 8, end of first paragraph, to the effect that the recording of baseline oxygen saturation was commenced with the second cohort.

13. The outcome of airway oedema is objective but what is not clear is how it is defined. How valid is this variable?

There is no formal grading system for- or definition of airway oedema. This variable is therefore subjective. However, subgroup analysis of the data shows that gradings of mild or severe oedema is strongly associated with hypoxaemia, which lends credence to the variability of this outcome. We have added a comment to the limitations section.

14. The information provided in the statistical methods regarding sample size is somewhat confusing. The numbers for the expected ratio between groups for the risk of desaturation require further explanation.

On page 4, paragraph 4, we state that the ratio and effect size was determined from the findings in the first cohort of 202 patients. A comment has been added in parenthesis to better clarify the ratio to which the reviewer alludes.

Reviewer #2:

The authors have presented a registry database involving the risk factors for hypoxaemia with hypertensive disease of pregnancy. The centres have a relatively high incidence of HDP making this an interesting interpretation with higher event rate. There are several concerns:

P3L12. HDP are associated with airway oedema and pulmonary oedema. Were there any auscultation findings in this registry data? This could be a more direct relationship due to preeclampsia from "anatomical" abnormality related to the disorder in particular pulmonary edema.

Auscultation findings were not recorded in the registry. As described above, in the second cohort of 200 patients we introduced the measurement of the baseline preoperative oxygen saturation, in order to detect patients with overt respiratory findings. It is unclear whether the reviewer is referring to overt pulmonary oedema or sub-clinical pulmonary interstitial oedema. Extensive experience and research in our facility has shown a high incidence of the latter. The possible association between pulmonary interstitial oedema and hypoxaemia is expanded upon in the Discussion.

P3L38. Clinically significant hypoxaemia was dichotomously defined as presence or absence of peripheral saturation below 90% during the intubation period starting from the time of intravenous induction of anaesthesia, to the Sp02 nadir observed prior to the maintenance phase of anaesthesia. The detection method will be important whether this is manually done or using monitoring data. There could be a higher bias to notice the lowest SpO2 in a medical condition such as preeclampsia?

The lowest observed value of SpO_2 was manually recorded and entered into the registry. Since the outcome assessors were unaware of the hypothesis and all patients undergoing general anaesthesia in obstetrics are at significant risk of hypoxaemia, we feel that measurement bias in the case of preeclampsia is unlikely. Automation of recording is certainly an option that is under consideration for future studies, but the infrastructure is currently lacking in our setting. We have added “observation and entry” to the risk of bias paragraph in the Discussion, page 8, paragraph 1.

P4L45. Patients with pre-existing chronic hypertension that did not progress to preeclampsia were not categorised as having HDP. What determines in the registry for determining that preeclampsia did not exist in the pre-existing chronic hypertension? The use of uric acid and liver function tests or other parameters?

The diagnosis of HDP was made by the obstetricians according to currently accepted international criteria. This has been emphasized in the Methods section, Page 4, paragraph 3.

P5L5. Quantile regression of SpO2 nadir was performed. Using the methods described, this would be an extension of linear regression that is used when the conditions of linear regression are not met (i.e.,

linearity, homoscedasticity, independence, or normality). The interpretation of the results would not be so direct.

> Quantile regression is a non-parametric regression model that allows a regression model of any percentile of the outcome distribution. The standard quantile regression is of the median (50^{th} percentile). The regression coefficients are the direct differences between the specific quantile for the groups in question, as well as slopes. Due to the restricted and non-normal distribution of SpO_2 nadir, the non-parametric regression model was used as our regression vehicle.

P6L16. In the subsequent 200 patients, hypoxaemia occurred in 16% with- and 11% without hypertension (P=0.317), This may suggest that the results may not be so robust as the results is dependent on the sampling. Are there any time-based differences in practice or demographic differences?

> We checked this aspect and found no suggestion of a time-based difference in demographics or practice. The summary of the data over time is shown in Supplementary Figure S1, as mentioned in paragraph 3 of the Results section. We further expand on this possible limitation in the Discussion. The slight increase in overall incidence of hypoxaemia suggests that results were not influenced by time-based changes in registry entries.

P6L23. The median (interquartile range [IQR]; range) SpO2 nadir in those with HDP was 98 (92 - 99; 15 - 100) compared to 98 (96 - 99; 51 - 100) in those without. Please do non-parametric testing of using all the values as there suggests bias in the distribution. A scatterplot would also be useful in this purpose.

> As stated in the text, HDP did not affect the 50th percentile (median) of SpO_2 (Supplementary Table S3 and S4). We have explicitly described the skewed distribution of saturation, which led to the use of the quantile regression (please see next point below for further detail). The quantile regression plots for each variable, as suggested by the reviewer, are to be found in section 5 of the Supplementary material.

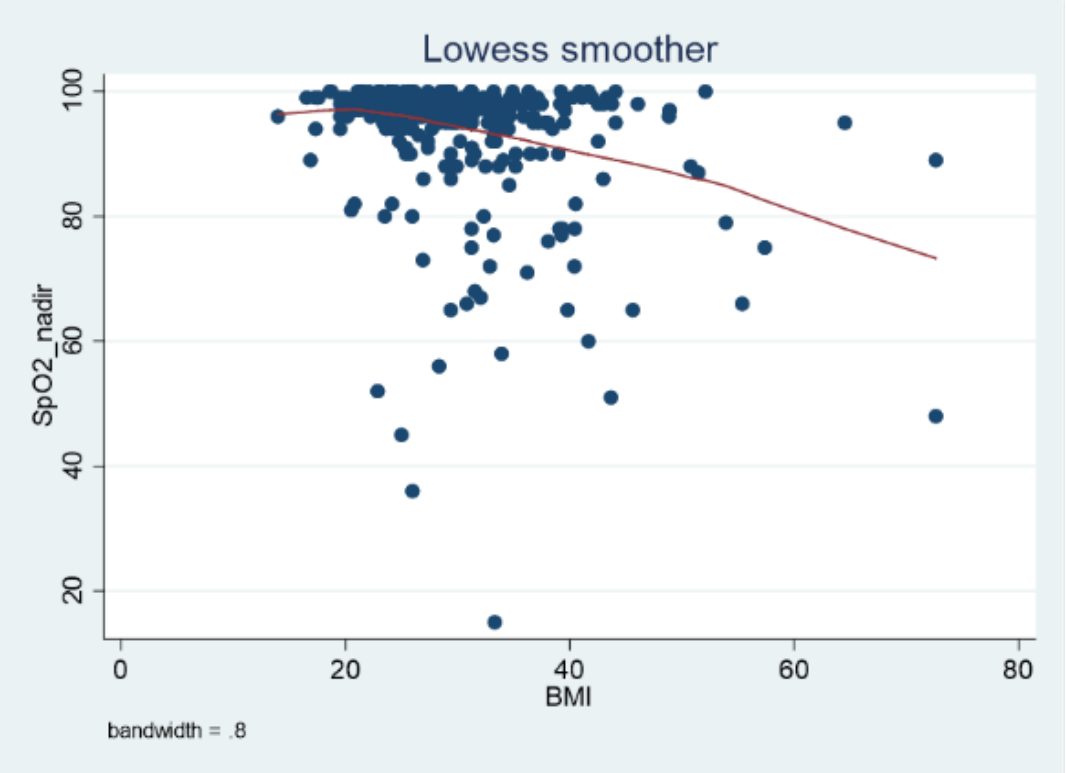
P6L27. Quantile regression analysis demonstrated that the presence of HDP is a predictor of the 25th percentile of SpO2 nadir. The distribution of the data of the lower 25% tile, would it suggest that not all the data points are being used? Clinically, how would the factors be used as there is high potential for confounders and mediators which is not surprisingly found in this paper.

Quantile regression of the 25% percentile is based on using the entire SpO_2 nadir distribution. and follows the same methodology as used for modelling the median (50th percentile). For modelling small percentiles (p5) one would need a large dataset to ensure that one has have enough values forming the lower end of the distribution. For p25 we have 25% of the data below this percentile, which is acceptable for the sample size of the current study.

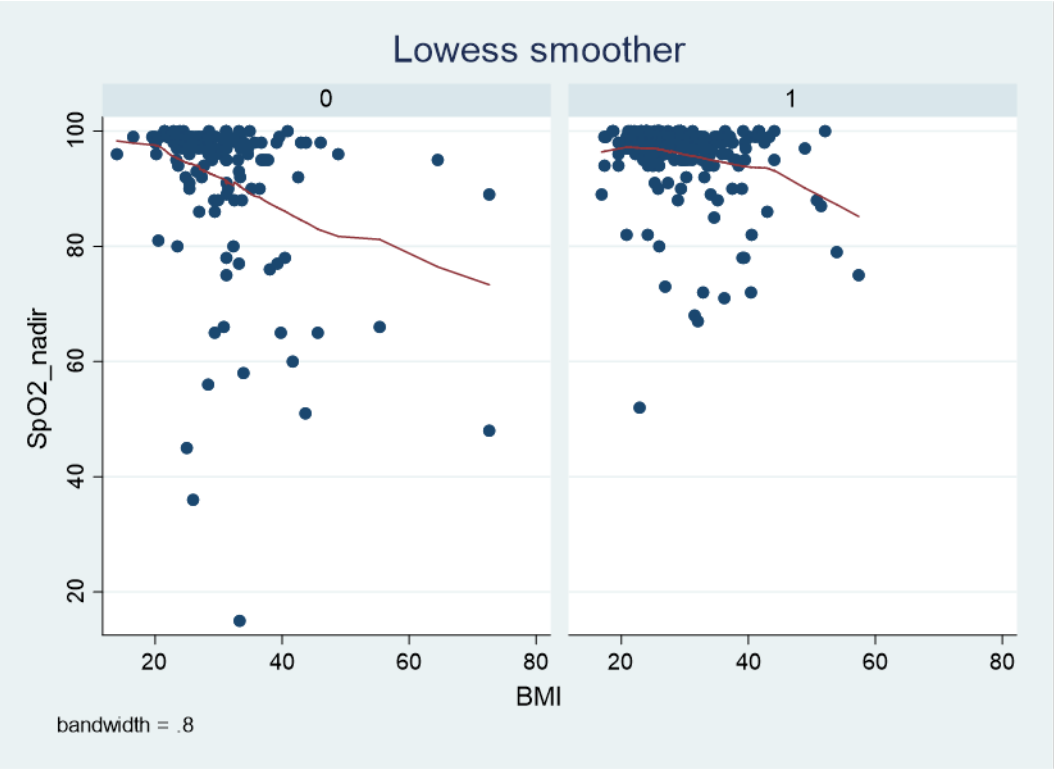
P6L30. Of the potential confounding variables, BMI was significantly associated with SpO2 nadir in the univariable analysis. The relationship of BMI in this model is unclear and the authors should clarify on the exact nature of the association in a multivariate model.

We did exploratory analysis of the association between BMI and SpO_2 nadir using a non-parametric lowess smoothing –see graphs below. From this work we used BMI as linear term in the regression models for both univariate and multivariate models. This approach, with the plots, is included in the Supplementary material (Section 5)

Overall:



By HDP group:



P6L33. The variables BMI and HDP were used in the multivariable and first order interaction models. The effects of BMI and HDP were synergistic in the interaction model. In the line with the previous comment, the clinical implication especially with continuous variable like BMI would be difficult to interpret rather than having a cut off.

We estimate the HDP effect at specific vales from the BMI, based on the overall regression model. This is statistically more efficient than categorising BMI. From the Figure, the range is within the BMI range seen in this setting.

P6L38. Airway oedema, number of attempts at tracheal intubation, Mallampati grade, and room air SpO2 had a mediating effect on the relationship between HDP and SpO2 nadir. The relationship statistically modelled is actually difficult to be interpreted clinically. Would the authors consider having a scoring system or propensity scoring so that a clinically relevant decision tree can be developed?

We agree with the reviewer that this could be a useful clinical tool, and are planning future studies to include larger numbers from the ongoing registry data set, to develop such a scoring system. However, this was an exploratory component of the analysis which was intended to be hypothesis-generating, and we thus felt that it was beyond the scope of the current study to attempt a more robust mediation analysis or emphasise this aspect in the manuscript.

Discussion: The authors summarized their findings with details of the model which makes interpretation in a clinically relevant situation difficult.

Our response is included in the next point, below.

P7L12. In lean patients (BMI ≤20 kg m-2), the 25th percentile for SpO2 nadir was not significantly different between those with or without HDP, but as BMI increased, the nadir became progressively lower in those with HDP. This particular cut-off would not be pragmatic for pregnancy as most patients would have a much higher BMI.

> We have estimated the effect sizes for a BMI range from 20 to 60 kg m^{-2}; we apologise for any confusion created by implying that there may be a "cut-off" value. Although the intention of the mediation analysis was to inform future investigation rather than clinical practice, following the reviewer's suggestion, we have provided pragmatic guidance in the text that the combination of BMI>30 kg m^{-2} and HDP should alert the practitioner to a clinically significant risk of hypoxaemia. For the non-HDP group, the BMI at 45 kg m^{-2} leads to saturation nadir below 90%.

P7L14. Mediation analysis supports the hypothesis that low baseline room-air saturation, the presence of airway oedema, increasing Mallampati grade, and the number of attempts required for intubation, are partly responsible for the effect of HDP on saturation nadir. The authors have not given either examples or decision tree models that would make the mediation analysis useful for clinicians.

> We feel that this is beyond the scope of this paper, but could be addressed in a future analysis of a larger registry data set.

The discussion should be centered on how this model would be or could be developed to reduce the risk of hypoxaemia. Would the authors be suggesting that all oxygenation procedures including the use of high flow nasal oxygen should be used for all patients with HDP or only a selected population?

> There is no current evidence to show that high flow nasal oxygen is effective in reducing hypoxaemia in obstetric general anaesthesia, although there is significant interest in exploring this issue in further studies. Our data suggests that there could be benefits in patients with HDP and/or raised BMI. At the current time, however, any conclusions as to the benefit of such an intervention would be speculative.

Table 5 should be provided with an example so that readers can see how the information can be applied in clinical practice.

> We understand the importance of providing clinical guidelines, but feel that we cannot make specific practice recommendations based upon purely observational data.

Response to second review – IJOA manuscript YIJOA-D-20-00209_R1

Handling editor comments (C. Wong):

Thank you for responding the reviewers' and my concerns and submitting your revised manuscript. You have largely resolved all concerns, but I have a few minor remaining questions, as does Reviewer #2 (below). Attached to this email are your text and table Word files. I have taken the liberty of using the Track Changes and Comment functions to suggest edits and embed queries. Please review the Track Changes. If you agree with them, please accept them. If not, please explain why you do not agree with the suggested change. Please respond to my Comments with the requested revision and/or by answering my question. Finally, please start with black font (change current red font to black) and note all new changes in red font.

> Thank you very much for your detailed and attentive review, and for the edited manuscript with tracked changes and comments. We have directly accepted the vast majority and responded to all comments/queries in the same fashion – please see the revised manuscript for the changes and responses. New changes other than your suggested edits have been changed to red font as per your instruction. (The previous changes were reverted to black font). We have also reformatted the tables as per your suggestions.

Reviewer #2:

On the question of overt pulmonary oedema or sub-clinical pulmonary interstitial oedema, (concern is whether there is an underlying mechanism of hypoxaemia in HDP, which will be useful in clinical practice. A consideration is whether in the future databases should include auscultatory findings or radiological findings. This may improve and develop a risk prediction model.)

> Overt pulmonary oedema in this setting is rare, but obvious when it occurs. We concur that clinical and/or radiological information regarding presence of subclinical pulmonary interstitial oedema would be very useful and will include this in future studies in the field. Indeed, we have both written about and published research on the cardiopulmonary interactions and use of perioperative point-of-care echocardiography in this setting (see *Hofmeyr R, Matjila M, Dyer R. Preeclampsia in 2017: Obstetric and Anaesthesia Management. Best Pract Res Clin Anaesthesiol. 2017 Mar;31(1):125-138. doi: 10.1016/j.bpa.2016.12.002. Epub 2016 Dec 18. PMID: 28625300* as well as *Ortner CM, Krishnamoorthy V, Neethling E, Flint M, Swanevelder JL, Lombard C, Fawcus S, Dyer RA. Point-of-Care Ultrasound Abnormalities in Late-Onset Severe Preeclampsia: Prevalence and Association With Serum Albumin and Brain Natriuretic Peptide. Anesth Analg. 2019 Jun;128(6):1208-1216. doi:10.1213/ANE.0000000000003759. PMID: 31094790*) We have included references to this work within the discussion. Where pulmonary alveolar oedema is suspected or diagnosed, it is our standard practice to perform point-of-care echo as part of the immediate management. Supplementary material from another recent paper from our department shows an uncommon case of severe systolic hypofunction in a woman with preeclampsia and pulmonary oedema which clearly demonstrates this phenomenon and application (see *Dennis AT, Dyer RA, Gibbs M, Nel L, Castro JM, Swanevelder JL. Transthoracic echocardiographic assessment of haemodynamics in severe pre-eclampsia and HIV in South Africa. Anaesthesia. 2015 Sep;70(9):1028-38. doi: 10.1111/anae.13038)*. However, we are not sure that this is within the scope of the current paper.

We estimate the HDP effect at specific vales from the BMI, based on the overall regression model. This is statistically more efficient than categorising BMI. From the Figure, the range is within the BMI range seen

in this setting. (I agree that using regression model would be statistically more efficient, but in clinical practice cut off scores will be more informative. Would suggest some comments on this).

We concur with the reviewer that "cut-off" values are easier to apply in clinical practice than a regression model. As per our previous responses to the initial review, this was an exploratory component of the analysis which was intended to be hypothesis-generating, and we thus felt that it was beyond the scope of the current study to attempt a more robust mediation analysis or emphasise this aspect too strongly in the manuscript. However, we are planning future studies to include larger numbers from the ongoing registry data set, to develop such a scoring system. On the previous revision, we have added a "cut-off" value of 30 $kg.m^{-2}$ above which risk of desaturation below 90% is increased in patients with HDP. We are loath to be too categorical when the core message is that practitioners should be much more attentive to preventing desaturation in patients with HDP, and particularly those with increased BMI. In light of this, we have added a statement to the text strengthening this concept.

Response to third review – IJOA manuscript YIJOA-D-20-00209_R2_CAW

Handling editor comments (C. Wong):

Thank you for your revised manuscript and your responses to my concerns and questions. You have largely resolved these concerns; there are a few minor, remaining concerns that should take you a few minutes to address. I moved a sentence from the Discussion to the Methods section, and this will require renumbering the reference citations. Also, the Supplemental tables were missing from the most recent submission. Please upload them with your revised manuscript.

Thank you, we have accepted the sentence moved from the discussion to methods section. The references have been updated and renumbered accordingly. Regarding the supplementary data: apologies, we misunderstood the instructions with respect to submitting content to Data in Brief and included the supplementary data files in the DiB zip folder. We will upload them separately again.

I have taken the liberty of editing your manuscript using Track Changes in the attached Word file. Please review the suggested changes and Accept them if you agree with them. If you chose not to accept a change, please indicate why you did not do so in your response letter. Note any additional changes by using red font. Please respond to my comments.

Thank you very much for your detailed and attentive review, and for the edited manuscript with tracked changes and comments. We have accepted and responded to all comments/queries in the same fashion – please see the revised manuscript for the changes and responses. New changes other than your suggested edits have been changed to red font as per your instruction (mostly the renumbering of references). (The previous changes were reverted to black font). We have also reformatted the tables as per your suggestions.

Appendix 4: IJOA Supplementary material

Data description

We present supplementary quantitative data from the first 402 cases recorded in an obstetric airway management registry. The clean dataset for the study has been made available online through ZivaHub (https://doi.org/10.25375/uct.11854752). The summary of trends in data over time (grouped into epochs of 100) is presented in Figure S1. Indications for general anaesthesia are reported in Table S1. Univariable quantile regression models for 25th and 50th percentile (median) of SpO_2 nadir are presented in Table S2 and S3. The multivariable quantile regression model for 50th percentile (median) of SpO_2 nadir is presented in Table S4 and the accompanying figures of quantile regression are displayed from Figure S2a to Figure S2r. The registry case report form (CRF) is attached for completeness.

Figure S1. Summary of trends in data over time. Registry data grouped in epochs of 100 cases.

Variation in the primary outcome. The crude risk of desaturation in those with hypertensive disorders of pregnancy (HDP) compared to those without HDP. Desaturation is defined as SpO_2<90%. N=396. HDP, hypertensive disorders of pregnancy; RR, relative risk.

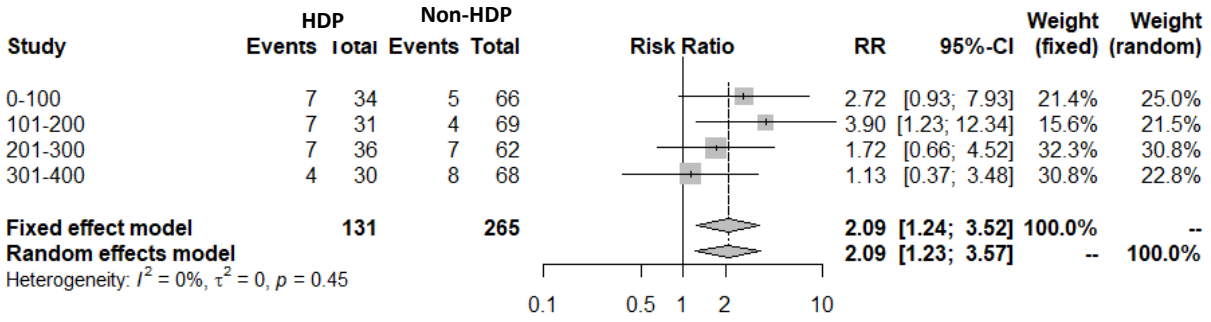


Table S1: Indications for general anaesthesia.

*Multiple indications for general anaesthesia accepted on case report form; HDP: hypertensive disorders of pregnancy; NVD: normal vaginal delivery; ICU: intensive care unit.

Indication*	HDP	Non-HDP	Total
Coagulopathy (suspected or confirmed)	65 (42.2%)	16 (5.6%)	81 (18.5%)
Severe fetal distress/bradycardia	27 (17.5%)	54 (19%)	81 (18.5%)
Failed neuraxial anaesthesia	13 (8.4%)	62 (21.8%)	75 (17.1%)
Prolonged general anaesthesia	-	13 (4.6%)	13 (3%)
Decreased level of consciousness	12 (7.8%)	1 (0.4)	13 (3%)
Abnormal placentation (abruptio placentae/ placenta praevia)	12 (7.8)	48 (16.9%)	60 (13.7%)
Other:			
Haemodynamically unstable	5 (3.2%)	11 (3.9%)	16 (3.7%)
Relook surgery	1 (0.6%)	3 (1.1%)	4 (0.9%)
Cord prolapse	1 (0.6%)	3 (1.1%)	4 (0.9%)
Fetal delivery complication (failed vacuum/instrument)	-	1 (0.4%)	1 (0.2%)
Breech/abnormal fetal presentation	-	1 (0.4%)	1 (0.2%)
Previous back surgery	-	4 (1.4%)	4 (0.9%)
Pre-existing medical disease (e.g. cardiac disease)	-	7 (2.5%)	7 (1.6%)
Evacuation of uterus	-	9 (3.2%)	9 (2.1%)
Uncooperative patient	2 (1.3%)	2 (0.7%)	4 (0.9%)
Bilateral tubal ligation post NVD	-	1 (0.4%)	1 (0.2%)
Third degree tear repair	1 (0.6%)	-	1 (0.2%)
Reintubation in ICU	1 (0.6%)	-	1 (0.2%)
Missing data points	14 (9.1%)	46 (16.2%)	60 (13.7%)
	154	284	438

Table S2: Univariable quantile regression model for 25th percentile of SpO_2 nadir.

Quantile regression of SpO_2 nadir was performed to identify confounding variables associated with, and mediators of, hypoxaemia. Due to the observation in the initial cohort that the presence of HDP specifically affects the lower end of the distribution of the SpO_2 nadir, the 25th percentile was modelled by quantile regression analysis using the Barrodale-Roberts method. If potential confounders were associated with the SpO_2 nadir in univariable analysis, they were included in the multivariable and interaction models.

	Estimate[a]	95% CI	p-value	MO
HDP (reference: non-HDP)	-4.00	-6.66 to -1.34	0.003	3
BMI	-0.38	-0.47 to -0.30	<0.0001	11
Gestation	-0.07	-0.22 to 0.09	0.41	26
Oedema: (reference: none)			<0.0001[c]	3
Oedema: Mild	-8.00	-11.45 to -4.55	<0.0001	
Oedema: Severe	-18.00	-26.61 to -9.39	<0.0001	
Attempts (reference: 1)			<0.0001[c]	3
Attempts 2	-24.00	-28.01 to -19.99	<0.0001	
Attempts 3	-60.00	-84.11 to -35.89	<0.0001	
TY (reference: < 1 year)			0.43[c]	3
TY 1 – 5 years	-3.00	-7.56 to 1.56	0.20	
TY > 5 years	-3.00	-7.97 to 1.97	0.24	
MP (reference: I)			0.047[c]	10
MP II	0.00	-2.95 to 2.95	1.00	
MP III	-1.00	-4.46 to 2.46	0.57	
MP IV	-8.00	-13.92 to -2.08	0.008	
Active labour (reference: not in labour)	1.00	-1.52 to 3.52	0.44	3
Room-air SpO_2	1	1	0	207[b]

[a]Estimates are interpretable as unit change in saturation per unit change in risk factor; [b]Room-air SpO_2 was only added to the dataset after the first 202 cases were recorded; [c]p-value for the likelihood ratio test. HDP: hypertensive disorders of pregnancy; BMI: body mass index (kg m^{-2}); MO: missing observations; TY: training years; MP: Mallampati.

Table S3: Univariable regression model for 50th (median) percentile of SpO_2 nadir.

	Estimate[a]	95% CI	p-value	MO
HDP (reference: non-HDP)	0.00	-2.08 to 2.08	1.00	3
BMI	-0.12	-0.16 to -0.09	<0.0001	11
Gestation	0.00	0.00	<0.0001	26
Oedema: (reference: none)			<0.0001[c]	
Oedema: Mild	-1.00	-3.79 to 1.79	0.48	3
Oedema: Severe	-9.00	-15.96 to -2.04	0.01	
Attempts (reference: 1)			<0.0001[c]	
Attempts 2	-3.00	-6.24 to 0.24	0.07	3
Attempts 3	-62.00	-81.49 to -42.51	<0.0001	
TY (reference: < 1 year)			0.43[c]	
TY 1 – 5 years	-1.00	-4.69 to 2.69	0.59	3
TY > 5 years	-1.00	-5.02 to 3.02	0.63	
MP (reference: I)			0.047[c]	
MP II	0.00	0.00	<0.0001	10
MP III	0.00	0.00	<0.0001	
MP IV	-4.00	-4.00 to -4.00	<0.0001	
Active labour (reference: not in labour)	0.00	-1.97 to 1.97	1.00	3
Room-air SpO_2	0.79	0.65 to 0.94	<0.0001	207[b]

[a]Estimates are interpretable as unit change in saturation per unit change in risk factor; [b]Room-air SpO_2 was only added to the dataset after the first 202 cases were recorded; [c]p-value for the likelihood ratio test. HDP: hypertensive disorders of pregnancy; BMI: body mass index (kg m^{-2}); MO: missing observations; TY: training years; MP: Mallampati.

Table S4: Multivariable quantile regression and interaction models for 50th percentile of SpO_2 nadir.

If potential confounders were associated with the SpO_2 nadir in univariable analysis, they were included in the multivariable model. Interaction between variables was tested in the final multivariable model. In mediation analysis, each mediator was individually tested in combination with HDP. If more than 10% relative change in the estimated association between HDP and SpO_2 nadir was seen, it was interpreted as having a significant effect.

Multivariable model: (HDP + BMI)	**Estimate[a]**	**95% CI**	**p-value**	**MO**
HDP (reference: non-HDP)	-0.38	-0.99 to 0.22	0.21	11
BMI	-0.13	-0.17 to -0.09	<0.0001	
Interaction model: (HDP x BMI)				
HDP (reference: non-HDP)	4.50	-3.17 to 12.18	0.25	
BMI	-0.00	-0.16 to 0.16	1.00	11
HDP:BMI	-0.19	-0.43 to 0.06	0.14	
Mediation analysis:				
HDP + RA SpO_2				
HDP (reference: non-HDP)	-0.78	-2.10 to 0.55	0.25	207[b]
SpO_2 (room air)	0.78	0.61 to 0.94	<0.0001	
HDP + Attempts				
HDP (reference: non-HDP)	0.00	-2.07 to 2.07	1.00	
Attempts (reference: 1)			<0.0001[c]	3
Attempts 2	-3.00	-6.24 to 0.24	0.07	
Attempts 3	-62.00	-81.49 to -42.51	<0.0001	
HDP + Oedema				
HDP (reference: non-HDP)	0.00	-2.22 to 2.22	1.00	
Oedema (reference: none)			<0.0001[c]	3
Oedema: Mild	-1.00	-3.95 to 1.95	0.51	
Oedema: Severe	-9.00	-16.08 to -1.92	0.01	
HDP + Mallampati				
HDP (reference: non-HDP)	0.00	0.00	<0.0001	
MP (reference: I)			0.050[c]	
MP II	0.00	0.00	<0.0001	10
MP III	0.00	0.00	<0.0001	
MP IV	-4.00	-4.00 to -4.00	<0.0001	

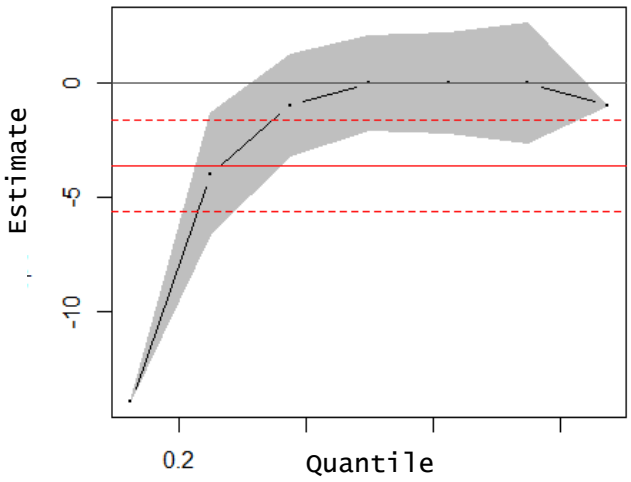
[a]Estimates are interpretable as unit change in saturation per unit change in risk factor; [b]Room-air SpO_2 was only added to the dataset after the first 202 cases were recorded; [c]p-value for the likelihood ratio test. HDP: hypertensive disorders of pregnancy; BMI: body mass index (kg m^{-2}); MO: missing observations; TY: training years; MP: Mallampati.

Figures of quantile regression (Figure S2a – S2r)

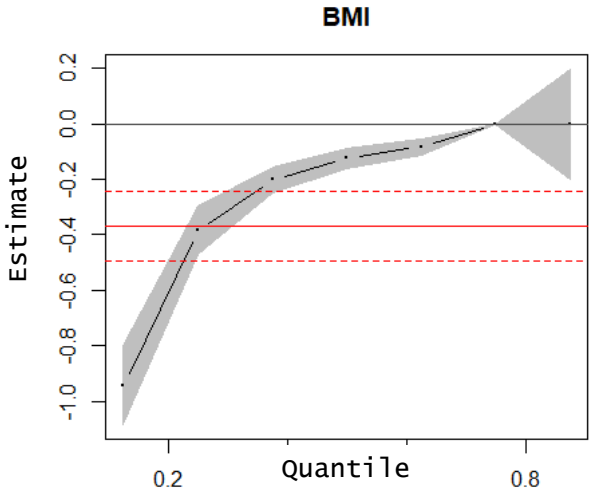
The figures should be read in conjunction with the regression tables. Estimates are interpretable as unit change in saturation per unit change in risk factor and presented on the y-axis. The 25th and 50th centile values can be found on the x-axis. Predicted values for the interaction model are also presented. The presence of active labour, gestational age and training years were not association with SpO2 nadir in the univariable analysis. These variables are thus not included in multivariable analysis. Therefore, BMI and HDP are the only variables in final multivariable model.

Univariable Quantile Regression of SpO2 nadir

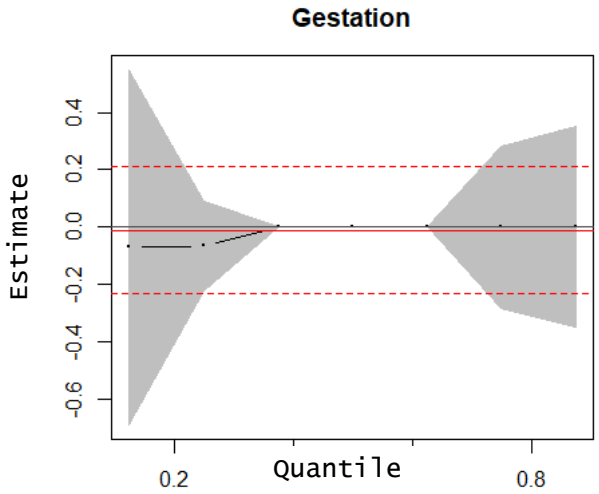
a) Hypertensive Disorders of Pregnancy (HDP)



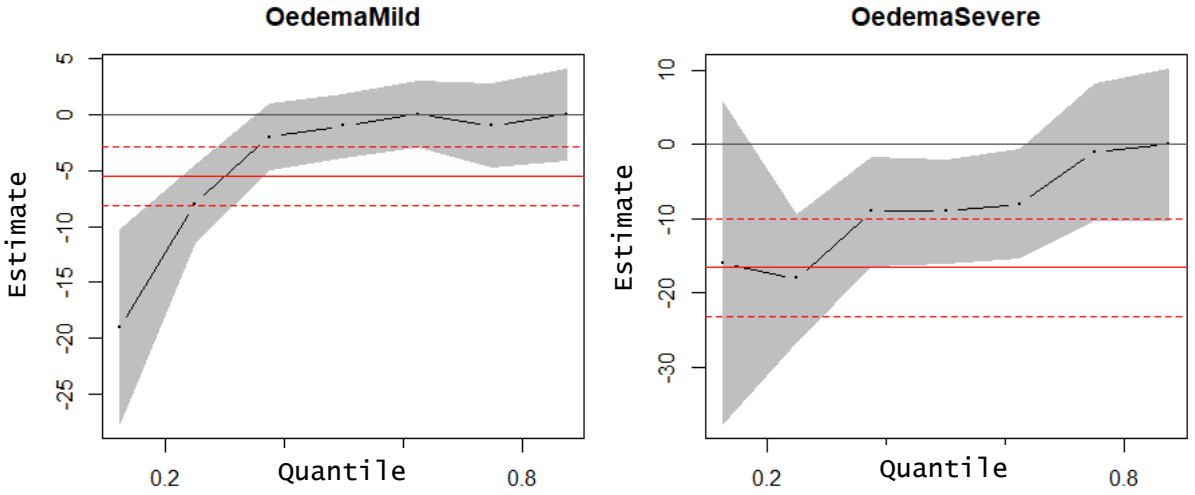
b) Body Mass Index (BMI)



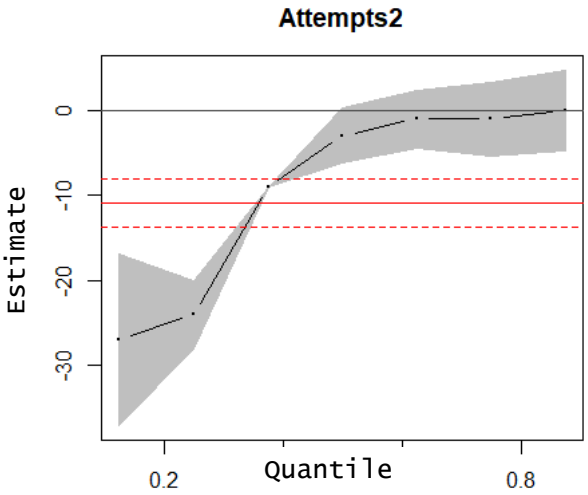
c) **Gestation**

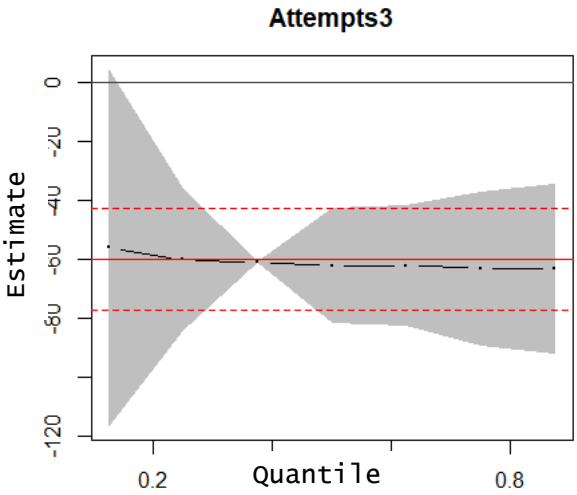


d) **Oedema**

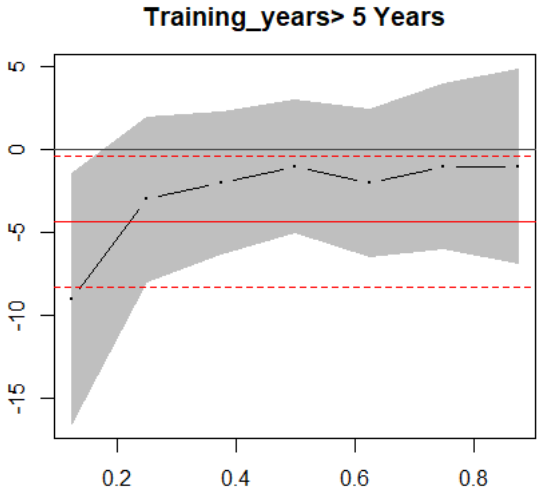


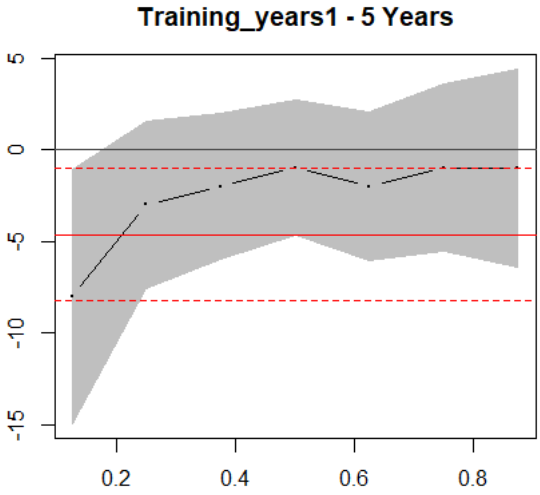
e) **Attempts**



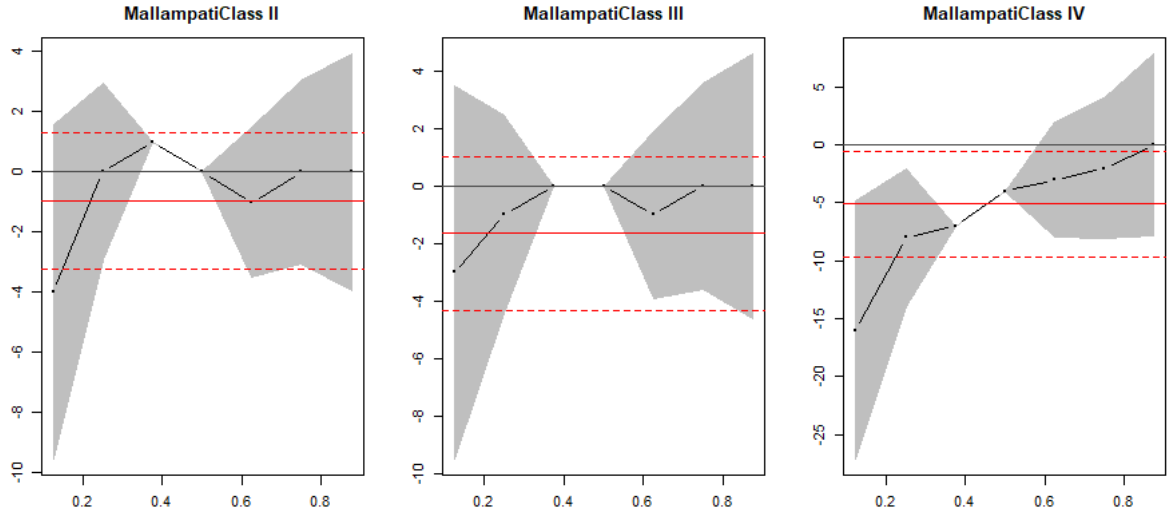


f) **Training years**

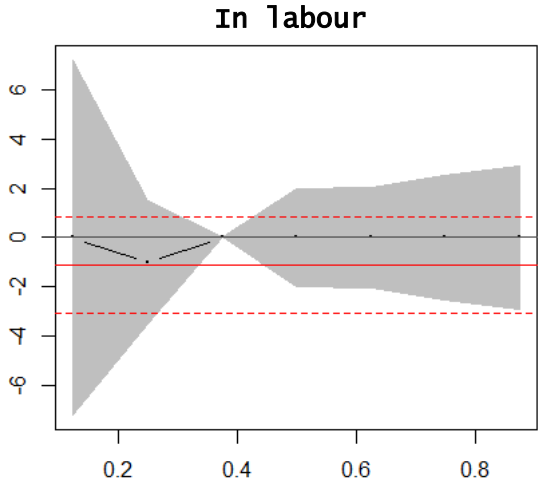




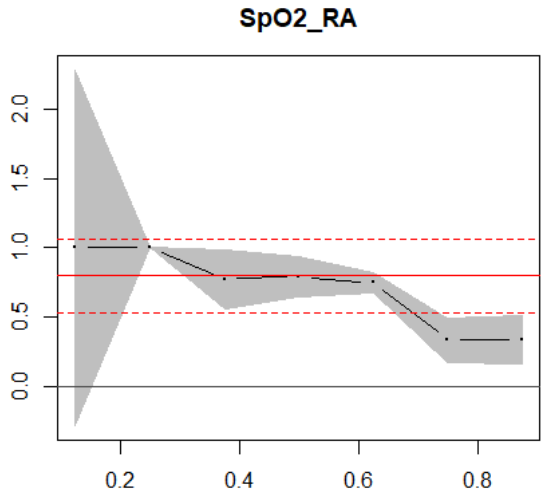
g) **Mallampati**



h) **The presence of active labour**

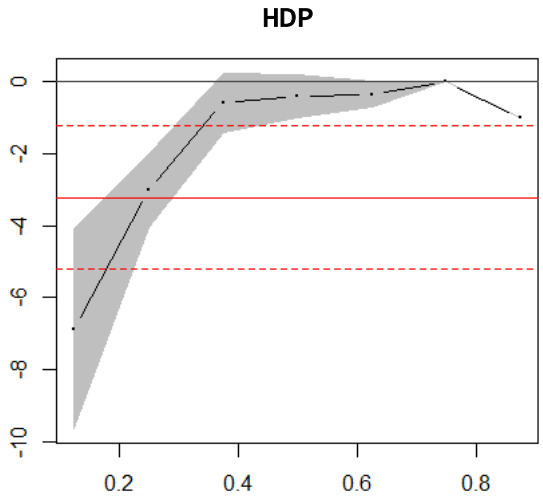


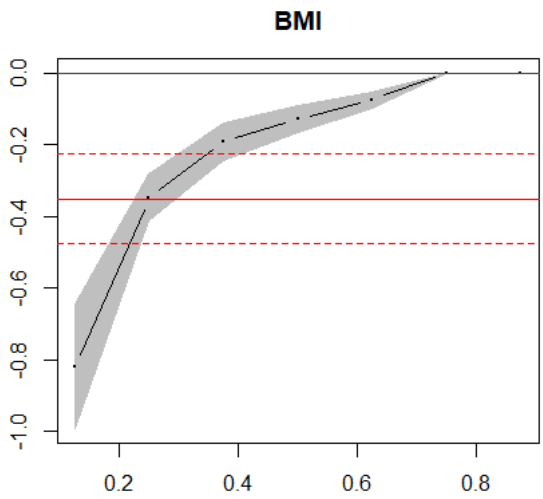
i) **Room air saturation**



Multivariable quantile regression of SpO2 nadir at p25; all 402 cases

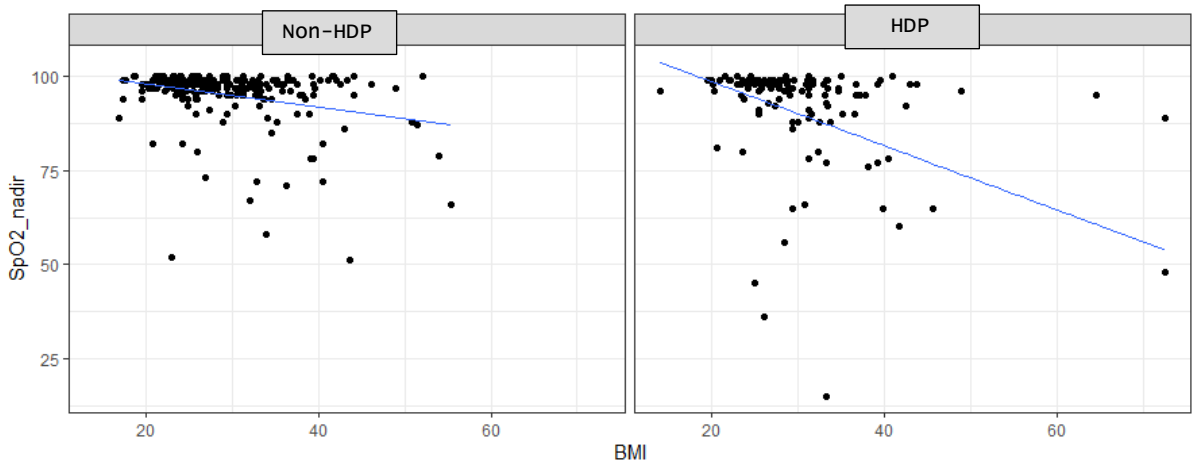
j) **HDP + BMI**



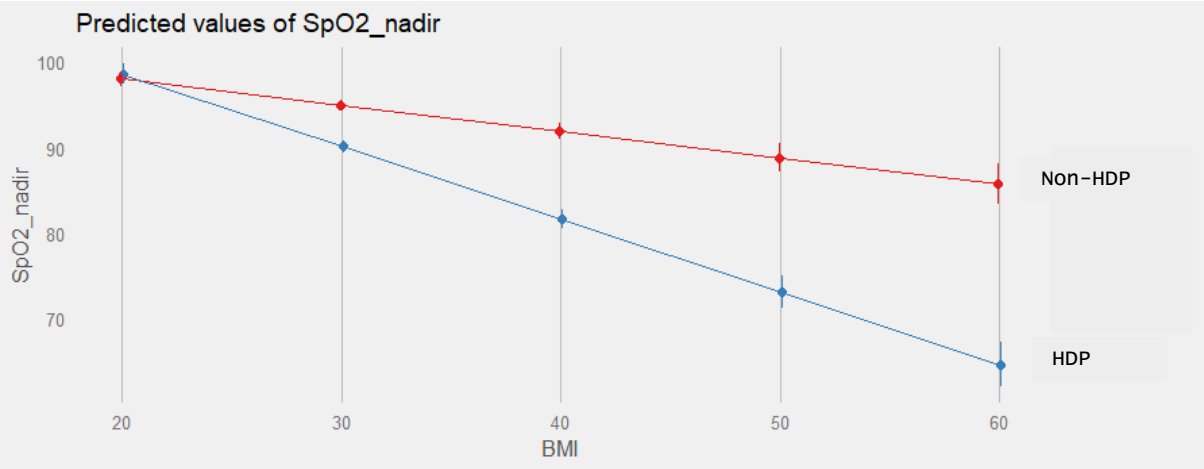


HDP * BMI (interaction)

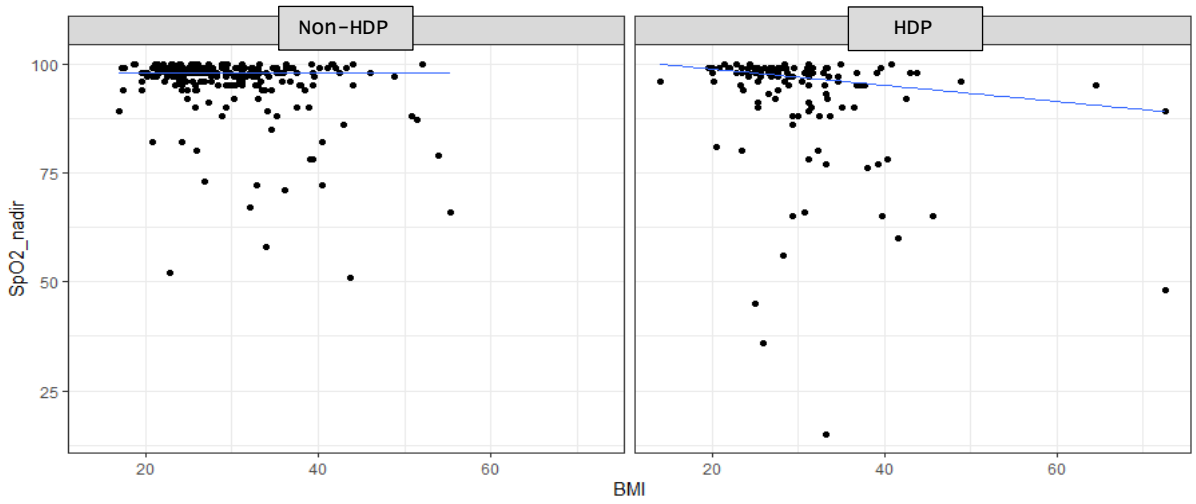
k) **Facetted scatter plot of SpO2 nadir interaction with BMI at p25 quantile regression line**



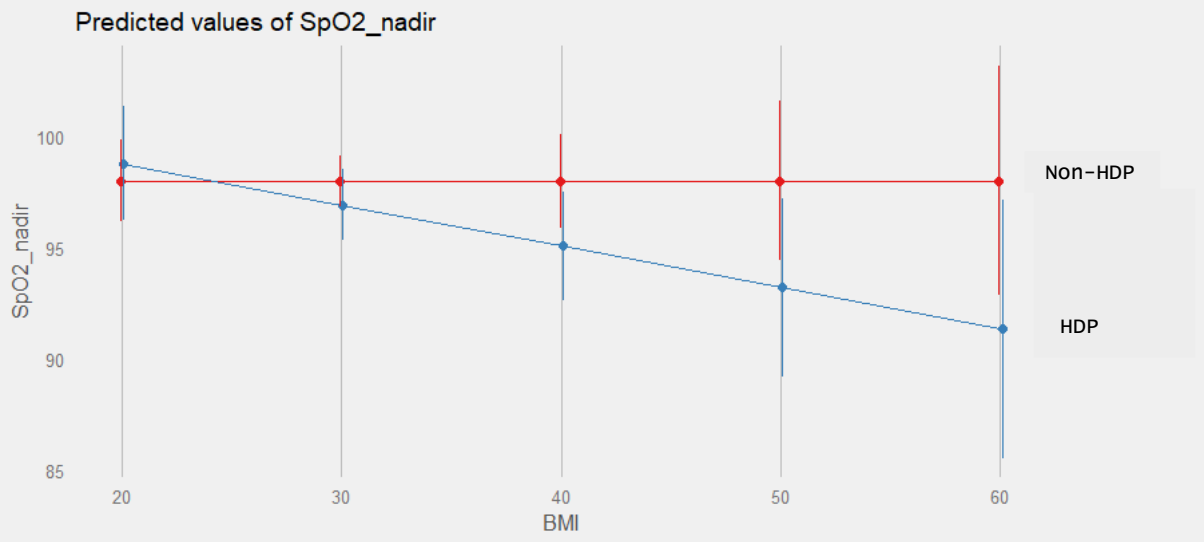
l) **Interaction plot of SpO2 nadir with BMI at p25 quantile regression line**



m) Facetted scatter plot of SpO2 nadir interaction with BMI at p50 quantile regression line

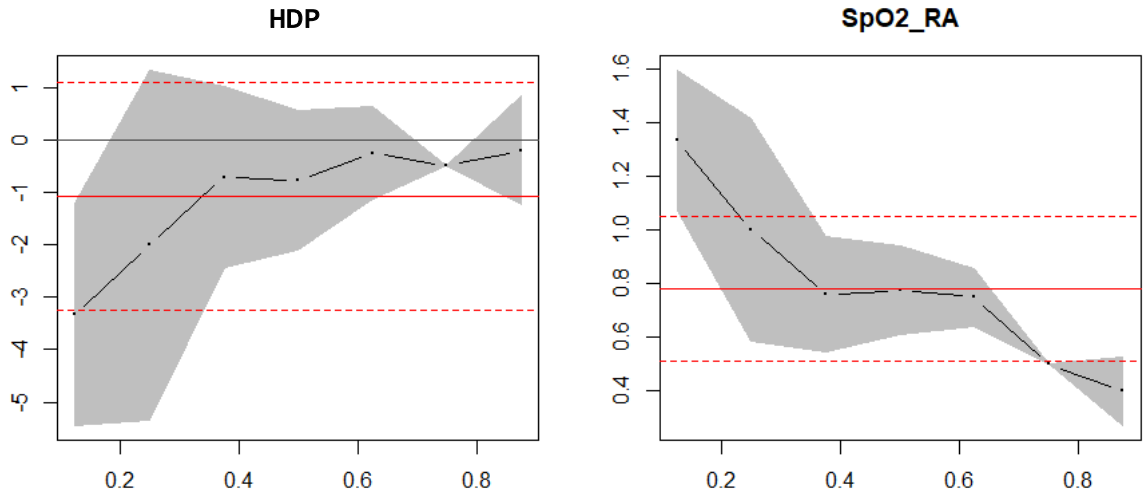


n) Interaction plot of SpO2 nadir with BMI at 50th quantile regression line

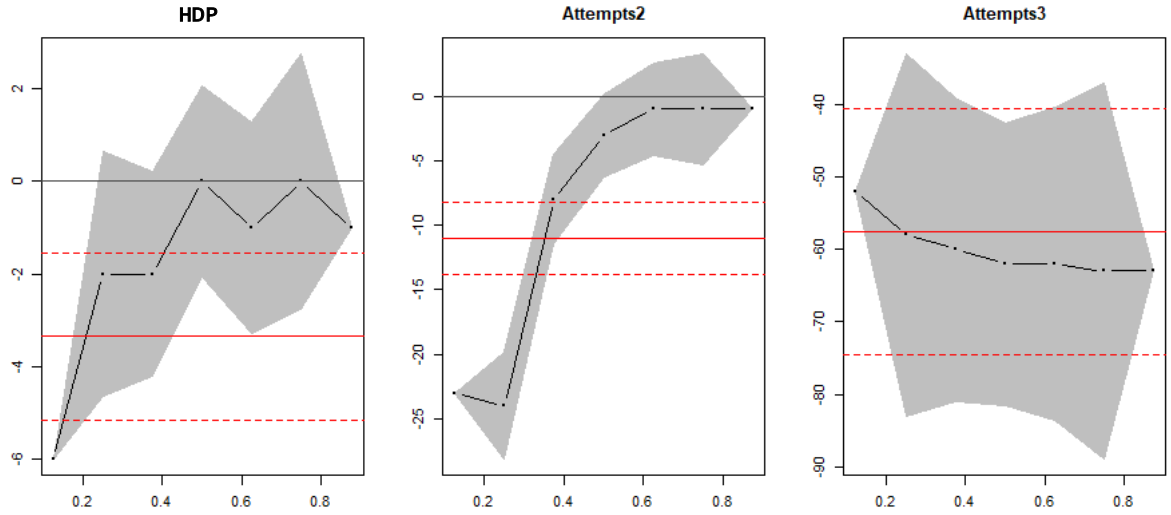


Mediation analysis

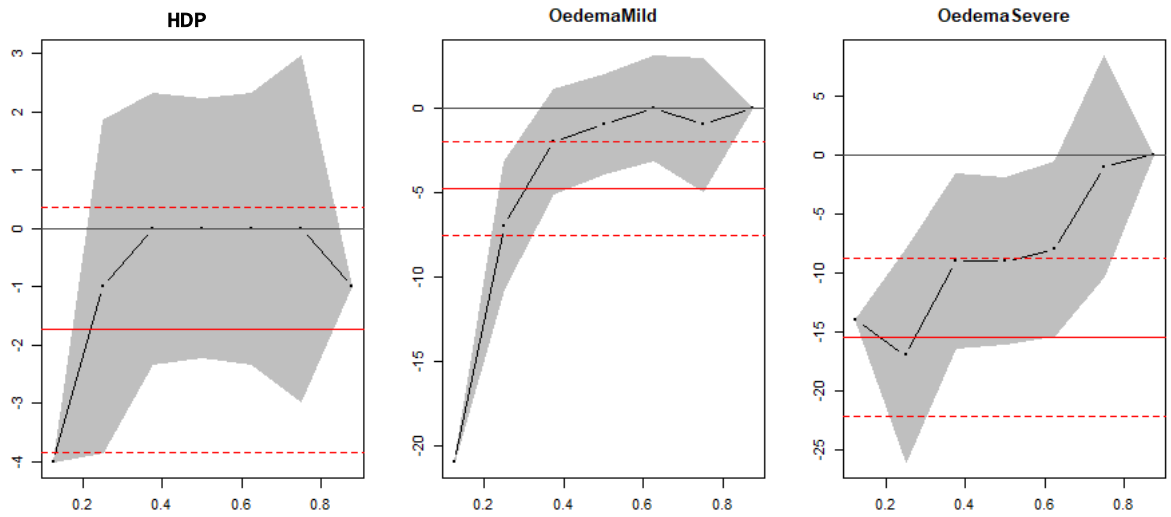
o) **HDP + room air saturation**



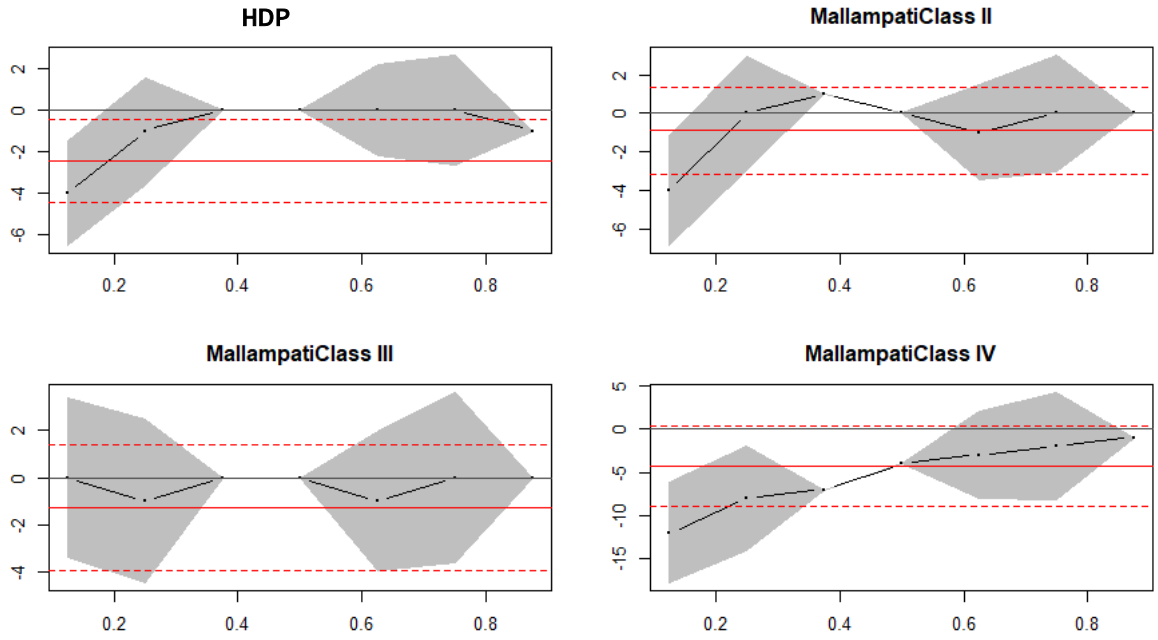
p) **HDP + number of attempts**



q) **HDP + Oedema**



r) **HDP + Mallampati**



Registry case report form (CRF)

Confidential

Obstetric Airway Management Registry

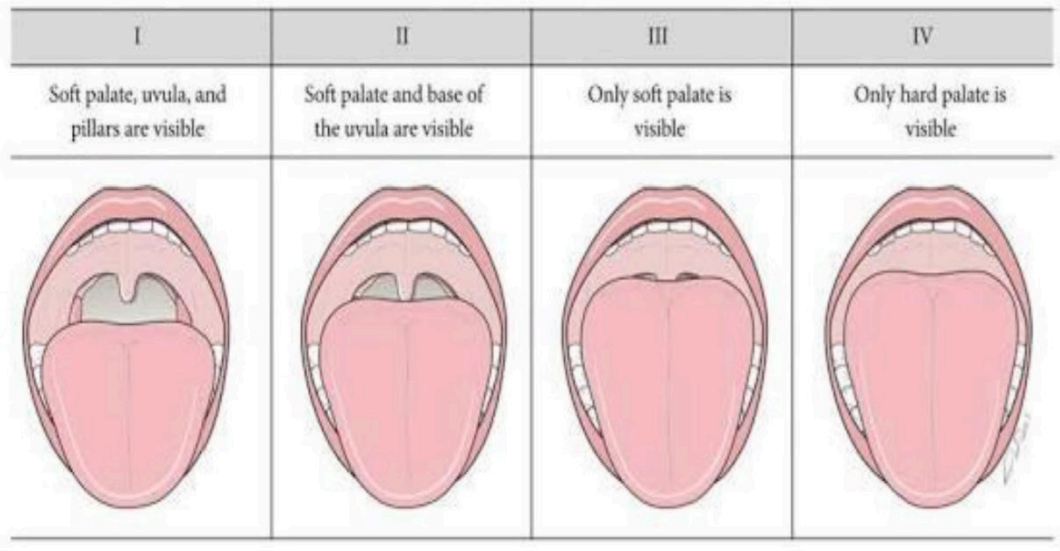
Thank you for completing this Obstetric Airway Management Registry (ObAMR). The data below should form part of your standard pre-operative assessment and peri-induction anaesthetic documentation, and should take 1-2 minutes per case to complete. Should you have questions, please contact Dr Maretha Smit (76177) or A/Prof Ross Hofmeyr (77392).

Please complete the survey below.

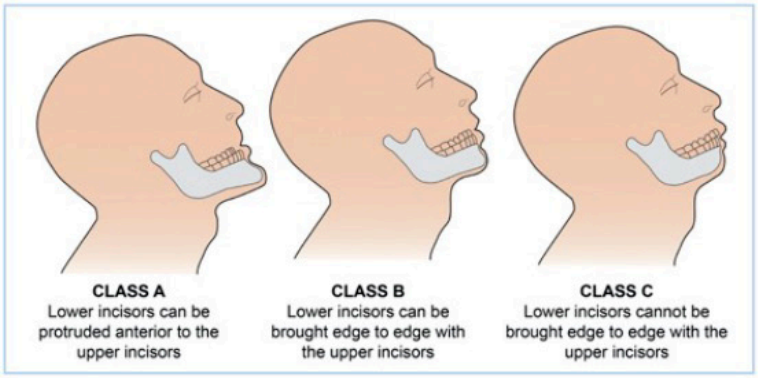
Case information	
Location	◯ GSH MK (Maternity Centre) ◯ GSH (Main Theatres) ◯ MMH (Mowbray Maternity) ◯ NSH (Somerset Hospital) ◯ MPH (Mitchells Plain Hospital)
Date	_____
What is your level of qualification?	◯ Intern ◯ Community service ◯ Medical Officer ◯ Registrar ◯ Consultant
Years of anaesthesia experience?	◯ < 1 Year ◯ 1 - 5 Years ◯ > 5 Years
Consent for use of data in registry	◯ Simple verbal consent obtained ◯ Patient unable* to provide sufficient verbal consent. Please flag for follow-up. (*Decreased level of consciousness etc)
Patient demographics	
Age of patient in years	_____
Height of patient in centimeters (actual or estimated)	_____
Body weight of patient in kilograms (actual or estimated)	_____

Obstetric history	
Gravidity of patient	_____
Parity of patient	_____
Current gestational age in weeks	_____
Hypertensive disease	◯ None ◯ Chronic hypertension ◯ Pregnancy induced hypertension ◯ Pre-eclampsia ◯ Pre-eclampsia superimposed on chronic hypertension ◯ Imminent eclampsia ◯ Eclampsia
Duration of labour	◯ Not in labour ◯ First stage (latent phase): from the onset of contractions to 3cm dilatation of the cervix ◯ First stage (active phase): from 3cm to full cervical dilatation ◯ Second stage: from complete dilation and effacement to delivery of the baby ◯ Third stage: from delivery of baby to delivery of placenta ◯ Fourth stage: the first hour after delivery ◯ Within 48 hours post delivery ◯ More than 48 hours post delivery

Anaesthetic Preassessment	
Primary anaesthetic strategy	◯ Neuraxial ◯ GA + mask ventilation ◯ GA + mask + supraglottic device ◯ GA + mask + endotracheal tube ◯ Other
Indication(s) for general anaesthesia	☐ Coagulopathy (or suspected thrombocytopaenia) ☐ Severe fetal distress/fetal bradycardia ☐ Inadequate neuraxial anaesthesia or 'failed spinal' ☐ Prolonged case ☐ Decreased level of consciousness ☐ Abnormal placentation (eg. praevia/accreta) ☐ Other (*Multiple answers accepted)
Please enter "Other" indication(s) for general anaesthesia:	_____ (Use only if your indication(s) are not listed in the previous question)
Mallampati score	◯ Class I ◯ Class II ◯ Class III ◯ Class IV ◯ Not assessed

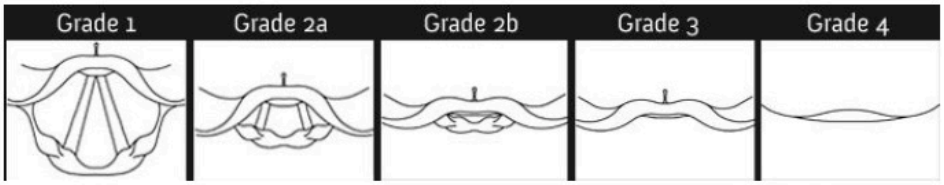


Dentition	◯ Full ◯ Partial - Most teeth present ◯ Partial - Most teeth absent ◯ Edentulous
Thyromental distance*	◯ ≥ 6,5cm or four fingers ◯ < 6,5cm or four fingers ◯ Not assessed (*The distance from the chin to the notch of the thyroid cartilage)
Mouth opening (inter-incisor gap)	◯ ≥ 5cm or three fingers ◯ < 5cm or three fingers ◯ Not assessed
Neck mobility* (atlanto-occipital extension)	◯ ≥ 35 degrees from neutral head position ◯ < 35 degrees from neutral head position ◯ Not assessed (*The range of extension of the head over the neck)
Mandibular protrusion	◯ Class A - the lower incisors can be protruded anterior to the upper incisors ◯ Class B - the lower incisors can be brought edge to edge with the upper incisors but not anterior to them ◯ Class C - the lower incisors cannot be brought edge to edge with the upper incisors ◯ Not assessed



Airway Management	
Room-air SpO2	_____ (*SpO2 breathing room air prior to preoxygenation)
Maximum SpO2 during preoxygenation prior to airway management	_____
Muscle relaxant used?	◯ None ◯ Suxamethonium ◯ Rocuronium ◯ Cisatracurium ◯ Other
Video laryngoscope immediately available?	◯ Yes ◯ No
Video laryngoscope used for intubation?	◯ Yes ◯ No
Intubation recorded on CMAC?	◯ Yes ◯ No
Patient positioning optimal* for intubation	◯ Yes ◯ No (*Ramped/sniffing/ear-to-sternal notch positioning)
Laryngoscope blade used	◯ Macintosh 3 ◯ Macintosh 4 ◯ CMAC 3 ◯ CMAC 4 ◯ CMAC D-blade ◯ None

Direct Cormack-Lehane view of the glottis	◯ Grade I - 50% or more of vocal cords visible ◯ Grade IIa - Less than 50% of vocal cords visible ◯ Grade IIb - Only arytenoid cartilages visible ◯ Grade III - Only the epiglottis is visible ◯ Grade IV - Epiglottis not visible ◯ Not assessed



Upper airway oedema?	◯ Absent ◯ Mild ◯ Severe
Intubation attempts	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ > 5 (*Number of times the laryngoscope blade was inserted into the mouth)
SpO2 nadir*	_____ (*lowest oxygen saturation during induction and airway management (%))
Introducer (bougie or stylet) used?	◯ Yes ◯ No
Supraglottic rescue (LMA or other) required?	◯ Yes ◯ No
Surgical airway rescue (front-of-neck access) required?	◯ Yes ◯ No

Appendix 5: IJOA Author guidelines

INTERNATIONAL JOURNAL OF OBSTETRIC ANESTHESIA
Official journal of the Obstetric Anaesthetists' Association (OAA)

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

- **Description** p.1
- **Impact Factor** p.1
- **Abstracting and Indexing** p.1
- **Editorial Board** p.2
- **Guide for Authors** p.3

ISSN: 0959-289X

DESCRIPTION

The *International Journal of Obstetric Anesthesia* is the only journal publishing original articles devoted exclusively to **obstetric anesthesia** and bringing together all three of its principal components; anesthesia care for **operative delivery** and the **perioperative period**, pain relief in **labour** and care of the critically ill obstetric patient.

- Original research (both clinical and laboratory), short reports and case reports will be considered.
- The journal also publishes invited review articles and debates on topical and controversial subjects in the area of obstetric anesthesia.
- Articles on related topics such as **perinatal physiology** and **pharmacology** and all subjects of importance to obstetric anaesthetists/anesthesiologists are also welcome.

The journal is peer-reviewed by international experts. Scholarship is stressed to include the focus on discovery, application of knowledge across fields, and informing the medical community. Through the peer-review process, we hope to attest to the quality of scholarships and guide the Journal to extend and transform knowledge in this important and expanding area.

IMPACT FACTOR

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PubMed/Medline
ScienceDirect
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EDITORIAL BOARD

GUIDE FOR AUTHORS

INTRODUCTION

Types of article

The International Journal of Obstetric Anesthesia welcomes original articles on **clinical topics**, **laboratory research**, **perinatal physiology** and **pharmacology**; and on all subjects of relevance and importance to obstetric anaesthesia. We welcome submissions related to global health, maternal safety and inequalities of care.

Original articles include randomised controlled trials, observational prospective and retrospective studies, meta-analyses, case-controlled studies, case series, systematic and narrative reviews. Short reports will also be considered for an original article when the aim, outcome and findings are presented succinctly with one illustrative Table or Figure. Each of these is associated with specific guidelines with regard to content and construct, such as provided by the CONSORT and STROBE guidelines. Please see Registration of clinical trials and journal governance. Int J Obstet Anesth 2014;23:204-5.

Submitting case reports

As discussed in Case reports and consent to publication. Int J Obstet Anesth 2016;28:1-2, the International Journal of Obstetric Anesthesia understands the importance of case reports in our sub-specialised field. To be accepted for publication, individual case reports need to have important and novel learning points; a simple narrative of a complex or challenging patient(s) or a patient with a rare condition is insufficient. Case series dealing with important areas of practice with a thorough review of the relevant literature will be considered. When writing the case report it is recommended that authors describe the salient features of the case, their novel clinical/technical solutions or features, and a short review of prior knowledge of these cases. Please see guidelines such as those at www.CARE-statement.org . Authors may choose to combine a number of similar cases (usually greater than 3) and write a case series and review article. Submissions of case reports, or correspondence in which a potentially identifiable patient is described, without written consent of the patient, will not be considered for publication (see Ethics in Publishing below).

Invited review articles

The journal publishes review articles and debates on topical and controversial subjects in the area of obstetric anaesthesia. Reviews are often commissioned, although authors may contact the Editor-in-Chief if they wish to discuss potential topics.

Surveys

Surveys will be considered provided they are likely to be of broad interest, well designed and conducted, adequately representative of the anaesthesia community, and have a response rate that is approximately 70% or more. Surveys with a lower response rate will be considered for publication as a letter or occasionally considered for publication as an article, depending on the importance of the topic surveyed and at the editors' discretion.

Contact details for submission

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- Full postal address

All necessary files have been uploaded:
Manuscript:
• Include keywords
• Include highlights - 3 to 5 bullet points, with no more than 85 characters each, including spaces.
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• All tables (including titles, description, footnotes)
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Graphical Abstracts / Highlights files (where applicable)
Supplemental files (where applicable)

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• Journal policies detailed in this guide have been reviewed
• Referee suggestions and contact details provided, based on journal requirements

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BEFORE YOU BEGIN

Ethics in publishing

Please see our information pages on Ethics in publishing and Ethical guidelines for journal publication.

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Informed consent and patient details

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Journal names should be abbreviated according to the List of Title Word Abbreviations.

Supplementary material

Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to supplementary material during any stage of the process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

Research data

This journal encourages and enables you to share data that supports your research publication where appropriate, and enables you to interlink the data with your published articles. Research data refers to the results of observations or experimentation that validate research findings. To facilitate reproducibility and data reuse, this journal also encourages you to share your software, code, models, algorithms, protocols, methods and other useful materials related to the project.

Below are a number of ways in which you can associate data with your article or make a statement about the availability of your data when submitting your manuscript. If you are sharing data in one of these ways, you are encouraged to cite the data in your manuscript and reference list. Please refer to the "References" section for more information about data citation. For more information on depositing, sharing and using research data and other relevant research materials, visit the research data page.

Data linking
If you have made your research data available in a data repository, you can link your article directly to the dataset. Elsevier collaborates with a number of repositories to link articles on ScienceDirect with relevant repositories, giving readers access to underlying data that gives them a better understanding of the research described.

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For supported data repositories a repository banner will automatically appear next to your published article on ScienceDirect.

In addition, you can link to relevant data or entities through identifiers within the text of your manuscript, using the following format: Database: xxxx (e.g., TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN).

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This journal supports Mendeley Data, enabling you to deposit any research data (including raw and processed data, video, code, software, algorithms, protocols, and methods) associated with your manuscript in a free-to-use, open access repository. During the submission process, after uploading your manuscript, you will have the opportunity to upload your relevant datasets directly to *Mendeley Data*. The datasets will be listed and directly accessible to readers next to your published article online.

For more information, visit the Mendeley Data for journals page.

Data statement
To foster transparency, we encourage you to state the availability of your data in your submission. This may be a requirement of your funding body or institution. If your data is unavailable to access or unsuitable to post, you will have the opportunity to indicate why during the submission process, for example by stating that the research data is confidential. The statement will appear with your published article on ScienceDirect. For more information, visit the Data Statement page.

AFTER ACCEPTANCE

Proofs
One set of page proofs (as PDF files) will be sent by e-mail to the corresponding author (if we do not have an e-mail address then paper proofs will be sent by post) or a link will be provided in the e-mail so that authors can download the files themselves. To ensure a fast publication process of the article, we kindly ask authors to provide us with their proof corrections within two days. Elsevier now provides authors with PDF proofs which can be annotated; for this you will need to download the free Adobe Reader, version 9 (or higher). Instructions on how to annotate PDF files will accompany the proofs (also given online). The exact system requirements are given at the Adobe site.
If you do not wish to use the PDF annotations function, you may list the corrections (including replies to the Query Form) and return them to Elsevier in an e-mail. Please list your corrections quoting line number. If, for any reason, this is not possible, then mark the corrections and any other comments (including replies to the Query Form) on a printout of your proof and scan the pages and return via e-mail. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. We will do everything possible to get your article published quickly and accurately. It is important to ensure that all corrections are sent back to us in one communication: please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

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AUTHOR INQUIRIES

Visit the Elsevier Support Center to find the answers you need. Here you will find everything from Frequently Asked Questions to ways to get in touch.
You can also check the status of your submitted article or find out when your accepted article will be published.

Appendix 6: Human Research Ethics Committee approvals

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Buildi
Groote Schuur Hospi
Observatory 79
Telephone [021] 406 66
Email: shuretta.thomas@uct.ac.
Website: www.health.uct.ac.za/fhs/research/humanethics/for

14 September 2018

HREC REF NO: R025/2018

A/Prof R Hofmeyr
Otolaryngology
H53, OMB

Dear A/Prof Hofmeyr

PROJECT TITLE: ***OBSTETRIC AIRWAY MANAGEMENT REGISTRY (ObAMR)***

Thank you for submitting your registry to the Faculty of Health Sciences Human Research Ethic Committee.

The HREC has **approved** the registration of your registry.

Please Note: All research, including that undertaken for a master's or doctoral degree, usin registered databases, registries and repositories, requires submission as a new study. It requires a application form (FHS013) and a protocol which has undergone departmental review. The study wi receive its own HREC REF number which will be linked to the main database or repository.

The registration of this registry is valid until **30 September 2021.**

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

29 May 2019

HREC REF: 341/2019

Prof R Hofmeyr
Department of Anaesthesia & Perioperative Medicine
D-23
NGSH

Dear Prof Hofmeyr

PROJECT TITLE: VALIDATION AND INITIAL DESCRIPTION OF THE PROSPECTIVE OBSTETRIC AIRWAY MANAGEMENT REGISTRY (ObAMR) [SUB-STUDY LINKED TO R025/2018]

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 May 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arlefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

29 May 2019

HREC REF: 342/2019

Prof R Hofmeyr
Department of Anaesthesia & Perioperative Medicine
D-23
NGSH

Dear Prof Hofmeyr

PROJECT TITLE: ObAMR-DESAT - DESATURATION DURING INTUBATION IN GESTATIONAL HYPERTENSION: AN ANALYSIS OF THE PROSPECTIVE OBSTERIC AIRWAY MANAGEMENT REGISTRY (ObAMR) MMED CANDIDATE DR M SMIT [SUB-STUDY LINKED TO R025/2018]

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 May 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Maretha Smit will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Appendix 7: NHRD registration

The National Health Research Database

Log off My Account (ross.hofmeyr@uct.ac.za) (/Manage) Help & Support (/Home/Help)

Home (/) Submit New Proposal (/Proposal/Create) Manage Proposals (/Proposal) Manage Researchers (/Researcher)

About (/Home/About)

Proposal Details: WC_201810_002

WESTERN CAPE HEALTH RESEARCH COMMITTEE

APPLICATION DETAILS

TITLE OF RESEARCH PROJECT

Obstetric Airway Management Registry (ObAMR)

TYPE OF STUDY

Non-academic

STATUS OF APPLICATION

Approved

STATUS OF PROJECT

On-Going

PROPOSAL SUBMISSION DATE

2018/11/16

You will find a list of all comments made on the selected research application. The list below displays comments visible to both the Applicant and Research Committee

COMMENTS

Comment	Comment Date	Comment By

PRIMARY INVESTIGATOR OF THE PROJECT/PROPOSAL

Title	Name	Surname	Role	Institution	E-Mail	Telephone No.	Mobile No.	CV/Resume
PROF	Ross	Hofmeyr	Principal Investigator		ross.hofmeyr@uct.ac.za	+27216504957	+27845499259	Download CV (/Researcher/Download/35468)

RESEARCH STAFF ASSIGNED TO PROJECT/PROPOSAL

Title	Name	Surname	Role	Institution	E-Mail	Telephone No.	Mobile No.	CV/Resume
DR	Maretha	Smit	Co-Investigator		marethas.smit@gmail.com		0825188673	Download CV (/Researcher/Download/35469)
PROF	Robert	Dyer	Principal Investigator		robert.dyer@uct.ac.za		0836002095	Download CV (/Researcher/Download/35470)

AIM AND OBJECTIVES

This registry will anonymously collate clinical information related to airway management during general anaesthesia, which is routinely recorded in the (paper) anaesthetic records. This will be used for quality control/assurance, to assess trends, and to plan for training, improvement of care, and future research.

STUDY AREA(S)/FIELD(S)

Description
Clinical
Health Systems
Non – Communicable Diseases
Women's Health

STUDY DESIGN(S)

Description
Descriptive
Observational Study
Quality Improvement

DATA COLLECTION METHOD(S)

Method Category	Method Description
QUANTITATIVE	Questionnaire

INTERVIEW REQUEST(S)

Position
No interview requests.

SAMPLE

All obstetric patients undergoing general anaesthesia at participating centers will be included.

DATA ANALYSIS TOOL(S)

Tool Description
Statistical Software Package (Eg. SPSS, STATA)

INFORMATION / DATA REQUEST ?

No

INFORMATION / DATA REQUEST DETAILS.

No Data Requested

LOCATIONS(S) WHERE STUDY WILL BE CONDUCTED

Facility

---- Paarl Hospital

---- Groote Schuur Level 3 Hospital

---- Mitchells Plain Hospital

---- Mowbray Maternity Hospital

---- Somerset Hospital

ANTICIPATED START DATE

2018/10/01

ANTICIPATED COMPLETION DATE

2021/09/30

INSTITUTION(S) WHICH GAVE ETHICAL APPROVAL

Institution

UCT - Faculty Of Health Sciences For Human Research Ethics Committee. University Of Cape Town

ETHICS APPROVAL NUMBER

HREC R025/2018

DATE OF ETHICAL APPROVAL

2018/09/14

DATE ETHICAL APPROVAL EXPIRES

2021/09/30

IF CLINICAL TRIAL, MCC APPROVED

No

NATIONAL CLINICAL TRIALS REGISTRY NUMBER

No Clinical Trial

FUNDING SOURCE

None

BUDGET (IN ZAR)

0 - 1 000

Back to List (/Proposal)

Appendix 8: Institutional approvals

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
E-mail : Bernadette.Eick@westerncape.gov.za

Professor Ross Hofmeyr
Department of Anaesthetics & Perioperative Medicine

E-mail: Ross.Hoffmeyr@uct.ac.za

Dear Professor Hofmeyr,

RESEARCH PROJECT: REGISTRY: - Obstetric Airway Management Registry (ObAMR)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 September 2021.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Kindly submit a copy of the publication or report to this office on completion of the research.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 3 October 2018

C.C. Mr L. Naidoo
Dr S. Peters
Dr T. Numanoglu
Professor J. Swanevelder

Western Cape Government
Health

Mowbray Maternity Hospital
Obstetrics Department

Reference: Letter
Enquiries: Dr. CJ. Stewart
Date: 09 October 2018

Professor Ross Hofmeyr
Department of Anaesthetics & Perioperative Medicine
Email: Ross. Hofmeyr@uct.ac.za

Dear Professor Hofmeyr

Research project: Obstetrics Airway Management Registry

You are granted permission to proceed with your research at Mowbray Maternity Hospital until 31 October 2020.

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with your research.
c) No additional costs to the hospital should be incurred.
d) As there is only one records clerk, folder requests should be given two weeks in advance, and no pressure should be applied for a quick service.
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the researcher with a copy of this letter as verification of approval.
g) Confidentiality must be maintained at all times.
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) On completion of your research, please forward any recommendations/findings that can be beneficial in terms of further action, development or policy review.
j) Please forward a copy of the publication or report on completion of the research.

Good Luck with your project

Yours Sincerely

Dr. Chantal Stewart
MMH Research Committee
9/10/2018

Appendix 9: ObAMR theatre checklist

Obstetric Airway Management Registry (ObAMR)

HREC R025/2018

All obstetric general anaesthetics should be included

Verbal consent checklist – kindly inform the patient of the following:

- ✓ Anonymous information and pictures will be collected
- ✓ The research involves no risk to the patient
- ✓ Participants should be granted the opportunity to be excluded from the study
- ✓ The waiver will not adversely affect the participant's welfare and rights
- ✓ No deviation from routine standard care will be provided

Scan the QR code or type the URL into your browser to complete the data capture form:

https://tinyurl.com/ObAMR

https://redcap.uct.ac.za/surveys/?s=3M77NTE9W3

Contact details:

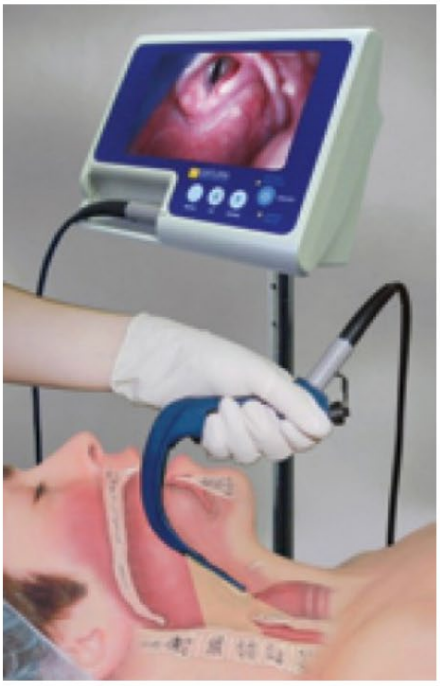
Maretha Smit – 082 518 8673 (76177)

Ross Hofmeyr – 084 549 9259 (77392)

Appendix 10: ObAMR patient information poster

All pregnant mothers

Did you know?
You may need a general anaesthetic if your baby is delivered by caeserian section



Difficult intubation has been reported in up to 1 in 20 pregnant women

Video laryngoscopes provide a better view of the larynx and may increase the success rate of first time intubations

We are collection anonymous information and pictures for a study to help us improve our clinical practice

If you would like to be excluded from this study, please ask your doctor to phone Dr. M Smit (76177)

HREC no: R025/ 2018

DEPARTMENT OF ANAESTHESIA & PERIOPERATIVE MEDICINE
UNIVERSITY OF CAPE TOWN

Appendix 11: STROBE checklist

Desaturation during tracheal intubation in patients with hypertensive disorders of pregnancy: an analysis of a prospective obstetric airway management registry

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	X
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	X
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	X
Objectives	3	State specific objectives, including any prespecified hypotheses	X
Methods			
Study design	4	Present key elements of study design early in the paper	X
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	X
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X
Bias	9	Describe any efforts to address potential sources of bias	X
Study size	10	Explain how the study size was arrived at	X
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	X
		(*b*) Describe any methods used to examine subgroups and interactions	X
		(*c*) Explain how missing data were addressed	X
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	X
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X
		(b) Give reasons for non-participation at each stage	X
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	X

		(b) Indicate number of participants with missing data for each variable of interest	X
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	X
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X
		(*b*) Report category boundaries when continuous variables were categorized	X
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	X
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	X
Discussion			
Key results	18	Summarise key results with reference to study objectives	X
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X
Generalisability	21	Discuss the generalisability (external validity) of the study results	X
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Contact information

Maretha Isabel Smit

maretha.smit@uct.ac.za

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