Original Article

Relationship between maternal arterial and foetal cord carbon dioxide tension and neonatal outcome in critically ill pregnant women at delivery

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ABSTRACT

Background and Aims: No studies have evaluated the relationship between maternal arterial partial pressure of carbon dioxide ($mPaCO_2$) and umbilical cord venous partial pressure of carbon dioxide (PCO_2) in critically ill pregnant women at delivery. Based on the studies in healthy pregnant women, an $mPaCO_2$ target of $\leq$50 mmHg is a suggested threshold during mechanical ventilation in critically ill parturients. We evaluated the relationship between $mPaCO_2$ and neonatal cord gases in critically ill parturients at delivery as the primary objective. The relationship between $mPaCO_2$ and APGAR scores at delivery was also analysed as a secondary objective. **Methods:** Maternal and neonatal cord gas data at delivery and APGAR scores were obtained by a retrospective chart review of 25 consecutive parturients with severe respiratory compromise who were delivered during mechanical ventilation. Linear regression was used to assess the relationship between $mPaCO_2$ and umbilical artery and vein PCO_2 and between $mPaCO_2$ and APGAR scores at 1 and 5 min. **Results:** There was a positive correlation between $mPaCO_2$ and neonatal cord venous PCO_2 (P = 0.013). Foetal venous PCO_2 exceeded predelivery $mPaCO_2$ by 17.5 (7.5) mmHg. There was an inverse relationship between $mPaCO_2$ and neonatal APGAR scores at 1 and 5 min (P = 0.006 and P = 0.007, respectively). **Conclusion:** Foetal cord venous PCO_2 can be predicted if $mPaCO_2$ values are known. Unlike in healthy pregnant women, there was an inverse relationship between rising $mPaCO_2$ levels and neonatal APGAR scores in critically ill pregnant women who had several associated compounding factors.

Keywords: APGAR score, artificial, carbon dioxide, critical illness, infant, linear models, newborn, pregnancy, respiration, umbilical arteries

INTRODUCTION

Permissive hypercapnia remains controversial in parturients with severe acute respiratory distress syndrome (ARDS). Based on very scant data, the maternal arterial partial pressure of carbon dioxide ($mPaCO_2$) has conventionally been recommended to be maintained below 50 mmHg.[1] Such a threshold was reported by observations of transient hypercarbia in healthy parturients undergoing vaginal delivery with methoxyflurane anaesthesia.[2] The transient hypercarbia was beneficial and resulted in babies born with good APGAR scores.[2] The applicability of these data to critical illness and mechanical ventilation is unclear. Thus, while it is known that maternal hyperventilation can lead to foetal hypoxaemia, the effects of hypoventilation remain unknown.[3] There are no studies where the foetal blood gas data was evaluated against the $mPaCO_2$

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status at the time of the delivery in critically ill pregnant women requiring mechanical ventilation. In addition, no studies have assessed the relationship between $mPaCO_2$ and APGAR scores at delivery in critically ill pregnant women. Furthermore, little relevant data is available to guide ventilation management during ARDS in pregnant patients, and lung protective ventilation strategies have not been assessed in pregnancy.[3]

We evaluated the relationship between $mPaCO_2$ and umbilical cord venous and arterial gases at delivery in critically ill pregnant women during mechanical ventilation as the primary outcome. The relationship between $mPaCO_2$ and APGAR scores was also analysed as a secondary outcome.

METHODS

This retrospective study was conducted after obtaining approval from the Institutional Review Board (IRB) of the University of Maryland, Baltimore, MD, USA (vide approval number HP-00091060, dated 6 May 2020). The IRB waived the written informed consent. This retrospective study included all pregnant patients with severe ARDS, admitted from March 2020 through January 2022, who delivered on mechanical ventilation and/or venovenous extracorporeal membrane oxygenation (VV-ECMO).

Lung protective ventilation strategies that followed the ARDS network protocol were used in all parturients. The intensivist chose the ventilation mode (i.e., volume control, pressure control and pressure-regulated volume control). In addition, a proning protocol was used (16 h prone and 8 h supine). Neuromuscular blockade with cisatracurium or rocuronium was also utilised. For parturients whose ARDS worsened despite maximum ventilator settings, VV-ECMO or delivery was considered.

On admission, several critically ill pregnant women were observed to have metabolic acidosis. Since maternal acidosis (potential of hydrogen [pH]<7.25) is generally poorly tolerated by the foetus and progressive maternal acidosis portends the development of a non-reassuring foetal heart rate tracing, our practice is to temporise maternal acidosis by raising the maternal pH closer to 7.4 with intravenous infusion of sodium bicarbonate (150 mEq of sodium bicarbonate in 1 L of 5% dextrose in water).[4] Those with haemodynamic instability were administered weight-based norepinephrine infusions for a mean arterial pressure goal of greater than 65 mmHg. Parturients were placed on continuous external foetal heart monitoring, with a labour and delivery nurse present at the intensive care unit (ICU) bedside.

The following data were obtained from the electronic medical records: maternal demographics, ventilator/extracorporeal membrane oxygenation requirements, maternal serial arterial blood gases, neonatal cord gases, APGAR scores, neonatal oxygen requirement and length of neonatal ICU stay. In addition, we obtained maternal comorbidities, indication for delivery, mode and location of delivery, maternal haemodynamics, use of vasopressors, sodium bicarbonate, sedative medications, neuromuscular blockade and predelivery vital signs (pulse rate, blood pressure).

Linear regression was performed using R version 4.03 (R Core Team, Vienna, Austria) to assess the relationship among $mPaCO_2$, pH, arterial partial pressure of oxygen (PaO_2), bicarbonate and the corresponding variable of umbilical artery and vein (primary outcome). Linear regression was also used to examine the relationship between $mPaCO_2$ and APGAR scores at 1 and 5 min (secondary outcome). Linear regression and Pearson's correlation coefficients were used to investigate the correlation among $mPaCO_2$, norepinephrine dosage, number of days on a norepinephrine infusion and APGAR scores at 1 and 5 min. A Welch two-sample *t*-test was used to determine if there was any difference in 1- and 5-min APGAR scores with maternal norepinephrine use. Categorical variables were summarised with numbers and percentages, and continuous variables were described using mean and standard deviation. The median and interquartile range (IQR) were used to describe non-normally distributed variables.

There was no *a priori* power calculation or participant recruitment, and all eligible patients were included during the study period. The sample size was determined by the availability of data when this research was initially conceptualised. However, based on an earlier study of correlations between $mPaCO_2$ and cord venous partial pressure of carbon dioxide (PCO_2; $R = 0.81$) during elective caesarean in healthy pregnant women with two-tailed significance criteria of alpha = 0.05 and power = 0.80, the minimal sample size needed with this effect size is 8.[5] Our

correlations were lower in critically ill parturients than in historically healthy subjects.[5] With our observed $mPaCO_2$ and umbilical vein PCO_2 values (R = 0.55), a power calculation with the same alpha and beta values would have yielded a required sample size of 24, and we did have an adequate number of patients in our sample.

RESULTS

Twenty-five parturients were delivered while they were mechanically ventilated, with four (16%) on VV-ECMO. The primary cause of ARDS was coronavirus disease 2019. Seven of the women failed maximal high-flow nasal cannula settings. They were urgently taken to the operating room (OR) for planned tracheal intubation and initiation of mechanical ventilation, followed by immediate delivery of the neonate. The remaining 18 women were mechanically ventilated for 0–30 (IQR 8) days before delivery. Twenty-four parturients underwent caesarean delivery (CD), and one patient had a spontaneous vaginal delivery in the ICU. Seven CDs were performed emergently at the bedside in the ICU, and the remaining 17 CDs were in the OR. The major indications for delivery included worsening maternal respiratory status, non-reassuring foetal heart rate and foetal bradycardia. The gestational age at the time of delivery was 32.5 (3.4) weeks. Table 1 shows the maternal and neonatal data. Table 2 shows the predelivery maternal and cord gas values.

There was a positive relationship between predelivery $mPaCO_2$ and umbilical vein and artery PCO_2 [Figure 1a and b] R = 0.55 (R^2 = 0.26, P = 0.013) and R = 0.6 (R^2 = 0.328, P = 0.005). Umbilical cord venous PCO_2 exceeded predelivery $mPaCO_2$ by 17.5 (7.5) mmHg. Figure 1c and d shows a significant negative correlation between $mPaCO_2$ and APGAR scores at 1 min, R = –0.55 (R^2 = 0.268, P = 0.006), and APGAR scores at 5 min, R = –0.56 (R^2 = 0.284, P = 0.004). In our sample, an $mPaCO_2$ of 40 mmHg was associated with APGAR scores less than 4 and 6 at 1 and 5 min, respectively, while an $mPaCO_2$ of 45 mmHg was associated with APGAR scores less than 3 and 5 at 1 and 5 min, respectively.

APGAR scores at 1 and 5 min were also inversely associated with the nadir maternal PaO_2 at any time point between admission and delivery, R = 0.54 (R^2 = 0.259, P = 0.006) and R = 0.52 (R^2 = 0.243 and P = 0.007), respectively.

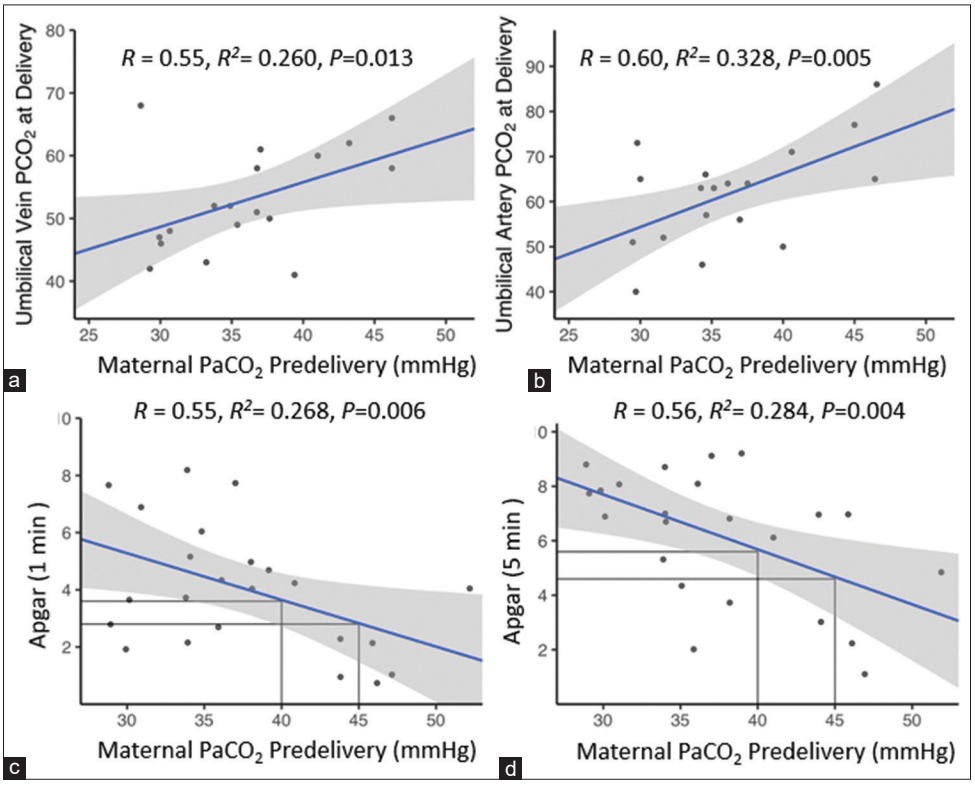

Figure 1: Linear regression models of the closest maternal partial pressure of arterial carbon dioxide ($PaCO_2$) to delivery with (a) umbilical vein partial pressure of carbon dioxide (PCO_2) at delivery, (b) umbilical artery PCO_2 at delivery and (c) APGAR scores at 1 min and (d) 5 min

Table 1: Maternal and neonatal characteristics

Maternal characteristics	Total parturients (*n*=25)
Maternal age (years), mean (SD) [range]	31 (6) [20–42]
Gestational age on admission (weeks.days), mean (SD) [range]	32.5 (3.4) [26.2–37.3]
BMI (kg/m^2), mean (SD) [range]	35.8 (6.6) [26.6–51.7]
Maternal length of stay (days), median (IQR)	20 (IQR 3.8–36.2)
Norepinephrine required	12
ECMO required	4
Days on ECMO before delivery, median (IQR)	32 (IQR 26–40.8)
Days on a ventilator before delivery, median (IQR)	13.5 (IQR 8.0–17)
Comorbidities	
Obesity	16
Advanced maternal age	10
Gestational diabetes	4
Type 2 diabetes	2
Chronic hypertension	1
Gestational hypertension	1
Preeclampsia	1
Mild asthma	5
Sickle cell disease	1
Sedation/analgesia	
Propofol	25
Etomidate	3
Dexmedetomidine	6
Midazolam	7
Fentanyl	14
Hydromorphone	3
Bicarbonate infusion	8
MAP range (low to high), mean (SD)	71 (7) to 95 (15)
Caesarean delivery	24
Delivery location	
Operating room	18
ICU bedside	7
Race/ethnicity	
African American	7
Asian	1
Hispanic or Latino	10
White	5
Other	2
Neonatal characteristics	**Total neonates (*n*=26)**
Weight at birth (g), mean (SD)	2034 (651)
NICU length of stay (days), median (IQR)	23 (IQR 11.3–34.3)
Respiratory support	
Intubation	13
CPAP	10
None	3
APGAR score	
1 min, median (IQR)	4 (IQR 2–5)
5 min, median (IQR)	7 (IQR 4.3–8.0)

Mean, SD or median (IQR Q1–Q3), except for categorical data presented as several patients. Norepinephrine infusions were weight-based dosing of 0.01–0.25 µg/kg/min. BMI=body mass index, CPAP=continuous positive airway pressure, ECMO=extracorporeal membrane oxygenation, ICU=intensive care unit, IQR=interquartile range, MAP=mean arterial pressure, NICU=neonatal intensive care unit, SD=standard deviation

There was no significant difference in APGAR scores at 1 or 5 min in parturients who required a norepinephrine infusion compared to those who did not. Furthermore, APGAR scores at 1 and 5 min did not correlate with the dosage or number of days of maternal norepinephrine usage.

DISCUSSION

A positive correlation between maternal and umbilical cord PCO_2 observed in this study reinforces earlier findings by Baraka,[5] Newman *et al*.[6] and Ivankovic *et al*.,[2] suggesting umbilical venous PCO_2 can be

Table 2: Maternal ABG and umbilical cord gases

	Umbilical artery	Umbilical vein	Maternal ABG predelivery
pH	7.22 (0.06) (7.19, 7.24)	7.26 (0.05) (7.24, 7.28)	7.37 (0.08) (7.33, 7.40)
Normal values	7.12–7.35	7.23–7.44	7.2–7.52
PO_2 (mmHg)	20.2 (5.15) (18.1, 22.2)	29.3 (13.2) (24, 34.6)	123.8 (39.4) (108, 139.5)
Normal values	6–27.6	16.4–40	80–100
PCO_2 (mmHg)	62.1 (10.9) (57.7, 66.5)	55 (11.8) (50.2, 59.7)	36.9 (6.9) (34.2, 39.7)
Normal values	41.9–73.5	28.8–53.3	28–32
HCO_3 (mmol/L)	24.7 (3.9) (23.1, 26.2)	24 (3.5) (22.6, 25.4)	20.8 (4.16) (19.1, 22.5)
Normal values	18.8–28.2	17.2–25.6	18–21

Data are Expressed as mean (standard deviation) (95% confidence interval). ABG=Arterial blood gases, PCO_2=Partial pressure of carbon dioxide, PO_2=Partial pressure of oxygen, pH: Potential of hydrogen, HCO3: Bicarbonate

predicted from $mPaCO_2$ status. However, our observed correlation in critically ill pregnant women was lower than that observed in healthy pregnant women during caesarean section. Newman *et al*.[6] determined the relationship between maternal capillary PCO_2 and foetal scalp PCO_2 in 68 healthy women during labour. The correlation coefficient was 0.476 ($P < 0.01$), akin to our findings. The foetal–maternal PCO_2 gradient during the first stage of labour was 8.8 mmHg; during the second stage, it was 15.3 mmHg. Five of these 68 healthy parturients were hyperventilated to induce maternal hypocarbia, and five inhaled 7.6% carbon dioxide in oxygen (carbogen) to induce hypercarbia. During hyperventilation, the foetal PCO_2 exceeded $mPaCO_2$ by 14 (range 8–21) mmHg (control 11.4 mmHg), while during carbogen inhalation, the foetal PCO_2 exceeded the maternal PCO_2 by 6.7 (range 2–22) mmHg (control 11.2 mmHg, maternal capillary $PaCO_2$ 43.8 mmHg during carbogen inhalation). Ivankovic *et al*.[2] studied the relationship between $mPaCO_2$ and foetal cord venous PCO_2 in healthy pregnant women at vaginal assisted delivery under methoxyflurane anaesthesia. Hypercarbia was induced in 15 women by removing a carbon dioxide circle absorber from the anaesthesia breathing system. Fifteen women had standard methoxyflurane anaesthesia with a circle absorber in place. The other 15 women had saddle blocks for vaginal assisted delivery. The mean cord blood venous PCO_2 and $mPaCO_2$ gradient was 8 mmHg in normocarbia pregnant women, 1 mmHg in the hypercarbia group ($PaCO_2$ = 57.6 [8.8] mmHg) and 4 mmHg in the saddle block group. On the contrary, in our study, the foetal cord venous PCO_2 exceeded $mPaCO_2$ by approximately 17.5 (7.5) mmHg, which is higher than the values observed by both Newman *et al*.[6] and Ivankovic *et al*.[2] in healthy pregnant women in labour. The exaggerated difference is most likely due to experimentally induced hypercarbia by carbon dioxide inhalation during normal labour in the above studies versus prolonged hypercarbia due to critical respiratory illness with other compounding factors such as infection in the parturients of this study. Nonetheless, the foetal blood gas PCO_2 is predictable from maternal PCO_2 values in critically pregnant women.

Neonatal outcomes were the secondary aim of our study. Maternal hypercarbia >45 mmHg at delivery may be associated with lower 1- and 5-min APGAR scores (<3 at 1 min and <5 at 5 min) [Figure 1c and d]. These findings suggest that the current threshold of permissive hypercarbia of a $PaCO_2$ of 50 mmHg may be too high, disrupting CO_2 elimination from the foetus, which has a limited ability to buffer excessive amounts of CO_2.[3,6] Our study's higher PCO_2 in the cord arterial blood demonstrates this.

The current threshold of $PaCO_2$ of 50 mmHg was extrapolated from Ivankovic *et al*.'s[2] study of iatrogenically induced transient (<10 min) hypercarbia up to 57 mmHg during methoxyflurane anaesthesia for vaginal assisted delivery as described above. Babies in the hypercarbia group had higher APGAR scores than those in the other groups. The higher APGAR scores were attributed to hypercarbia causing higher cardiac output, increased uteroplacental blood flow, relaxation of the uterus and a leftward shift of the oxyhaemoglobin dissociation curve.[2] Indeed, this study's conclusions did not apply to our study parturients with ongoing critical illnesses for an extended duration and necessitated administration of other concomitant drugs.[7] Concurrent medications, such as fentanyl, midazolam and propofol, are necessary to facilitate mechanical ventilation in the parturients, and these drugs affect the neonatal outcomes. Furthermore, the induced hypercarbia in the study of Ivankovic *et al*.[2] was transient compared to the relatively longer-lasting hypercarbia in our critically ill study population. Another case series reviewed five parturients with status asthmaticus, where $mPaCO_2$ ranged from 31 to

132 mmHg during pregnancy. However, the parturients with higher $PaCO_2$ were in early pregnancy (less than 14 weeks) and those beyond 27 weeks had normal $PaCO_2$. Therefore, the findings of this study do not apply to parturients requiring extended mechanical ventilation.[8]

It is indeed difficult to separate the effects of high maternal and foetal PCO_2 versus the impact of concomitant factors intrinsic to critical patients, such as drugs, infection and vasopressor support, on the neonatal outcome. However, it must be noted that many of the parturients with lower $mPaCO_2$ also received sedative drugs and vasopressor support. The aetiology of lower APGAR scores may be debatable. However, it is indisputable that clinicians must be prepared to expect babies with lower APGAR scores and to assist and support newborns with lower APGAR scores at delivery in critically ill pregnant women in whom $mPaCO_2$ is high.

Lower nadir predelivery maternal PaO_2 values during the period between admission and delivery also predicted lower APGAR scores at 1 and 5 min, suggesting oxygen delivery to the foetus is also a critical factor in the neonatal outcome. However, the PaO_2 value closest to delivery was within the normal range for all patients in our case series. Maternal pH did not predict APGAR scores, possibly due to the sodium bicarbonate infusions that normalise metabolic acidosis.

There were a few limitations of this study. This was a retrospective study with a small sample size. Several uncontrollable factors inherent to critically ill parturients influence neonatal APGAR scores. Many parturients received midazolam, fentanyl and propofol infusions for sedation while on mechanical ventilation, and these may affect the APGAR scores. Haemodynamic factors can also influence neonatal outcomes. While the parturients' haemodynamic parameters were maintained within a reasonable range, 48% of the women received norepinephrine infusion around or during the predelivery period. Extended use of vasopressors can influence uteroplacental blood flow and neonatal outcomes. However, no statistically significant relationship was found for maternal norepinephrine use, including when accounting for the dosage and days of norepinephrine usage. Furthermore, a large portion of patients in our series were African American (28%) and/or Hispanic (40%), which may be reflective of the racial/ethnic disparities in maternal morbidity and mortality.[9] Finally, we do not have data to inform conclusions on the possible implications for the long-term neonatal outcomes in babies with lower APGAR scores.

CONCLUSION

The $mPaCO_2$ predicts cord PCO_2 during mechanical ventilation of critically ill pregnant women. However, the difference between the two is exaggerated in this group of parturients. We found an inverse relationship between rising $mPaCO_2$ levels and neonatal APGAR scores, at least in critically ill pregnant women with many compounding factors.

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Conflicts of interest
There are no conflicts of interest.

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