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Original Research

A Cohort Comparison Study on Women in Threatened Preterm Labor Given Nifedipine or Nifedipine and Salbutamol Tocolysis in Air Medical Retrieval

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A B S T R A C T

Objective: Women with threatened preterm labor in remote Australia often require tocolysis in the prevention of in-flight birth during air medical retrieval. However, debate exists over the tocolytic choice.

Methods: A retrospective analysis was undertaken on data containing women who required air medical retrieval for threatened preterm labor within Western Australia between the years 2013 and 2018.

Results: A total number of 236 air medical retrievals were deemed suitable for inclusion; 141 received nifedipine, and 95 women received salbutamol + nifedipine. Tocolytic efficaciousness was reported in 151 cases, proportionally more ($P < .05$) from the women who received salbutamol + nifedipine ($n = 68$, 71.6%) compared with the women who received nifedipine only ($n = 83$, 58.9%). Those receiving salbutamol + nifedipine were more likely to suffer maternal tachycardia ($n = 87$ [91.6%] vs. $n = 62$ [44.0%]), fetal tachycardia ($n = 26$ [27.4%] vs. $n = 13$ [9.2%]), nausea ($n = 17$ [17.9] vs. $n = 5$ [3.55%]), and vomiting ($n = 12$ [12.6%] vs. $n = 2$ [1.4%]). Three women who received salbutamol + nifedipine had serious side effects including echocardiographic changes, chest pain, and metabolic and lactic acidosis.

Conclusion: Salbutamol + nifedipine tocolysis was proven to be more effective than nifedipine only. Although salbutamol + nifedipine had increased temporary side effects, most were nonsevere and managed in-flight.

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Rural and remote Australians have a higher incidence of social disadvantage and chronic disease prevalence coupled with a lower provision of health care compared with major city areas.¹ Women living in rural and remote areas are reported to have higher incidences of modifiable risk factors, such as tobacco smoking and alcohol

consumption, and higher rates of diabetes, hypertension, and renal disease.¹ These trends have been linked to adverse pregnancy outcomes, including threatened preterm labor (TPTL), compared with Australian averages.² The higher incidences of modifiable risk factors combined with an increased likelihood of TPTL, which is exacerbated by remoteness, are concerning because preterm birth is linked to an increased risk for long-term morbidities.¹⁻³ As such, many women who reside in rural and remote areas with high-risk pregnancies are advised to relocate to a metropolitan center before the expected birth date because of a lack of resources and specialized medical expertise,⁴ such as emergency cesarean services. However, relocation for many women is challenging, with some requiring emergency retrieval services.

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The primary aim of preventing TPTL is to delay birth to allow women to be transferred to an inner-regional or major city hospital. Outborn neonates (ie, born outside the tertiary setting) have far worse outcomes than inborn neonates (ie, born in the tertiary setting), including double the rates of stillbirth and neonatal death⁵ and long-term cognitive development delays.⁶ Nifedipine is typically the first drug of choice in TPTL management with the Royal Flying Doctor Service (RFDS) within Western Australia (WA) followed by intravenous salbutamol if nifedipine alone is ineffective. Salbutamol tocolysis is rarely seen in other Australian or international air medical and health care providers due to potential significant maternal risk factors, such as palpitations, tachycardia, nausea, hypotension, and headache.^{3,7} The literature also indicates that tocolysis therapy for TPTL and ruptured membranes does not improve adverse neonatal outcomes or time to delivery.^{8,9} As such, there is debate within the air medicine sector regarding the usefulness of tocolytic therapy, specifically that of intravenous salbutamol.

The aim of this study was to compare the efficaciousness of tocolytics in halting TPTL during air medical retrieval (AR), specifically between nifedipine only and salbutamol + nifedipine. We also aimed to determine any potential side effects during AR.

Materials and Methods

Setting

The Australian state of WA covers 2.5 million km², which is comparable to one quarter the size of Europe and one quarter the size of the United States. WA has a population of approximately 2.6 million people; 79% of people reside in Perth and the area southwest of Perth, and the remaining 21% of people are widespread across the state.¹⁰ The RFDS provides essential air medical and primary health care to populations who are unable to access specialist care.⁷

Sample

A retrospective analysis was undertaken on routinely collected data from a sample of women who required an AR for TPTL from rural WA between August 26, 2013, and December 23, 2018. TPTL is defined as the onset of regular painful uterine contractions (at least 1 every 10 minutes), which are associated with an effacement and/or dilatation of the cervix at under 37 weeks' gestation (see Figure 1).¹¹ Side effects were collated directly from the case notes when documented by the medical and nursing crew. For example, nausea or vomiting was coded accordingly. Maternal tachycardia was documented as a heart rate over 100 beats/min. Hypotension was defined as any maternal systolic blood pressure below 90. Similarly, fetal tachycardia was coded as any documented fetal heart rate over 160 beats/min.

The inclusion criteria were pregnant women 20 to 36 + 6 weeks' gestation who received an AR for TPTL. The lower gestation of 20 + 0 weeks was set to ensure no extreme threatened preterm labor transfers were omitted from our study. The exclusion criteria were women outside the viable preterm neonate age (< 20 weeks' gestation) and those not in established or threatened labor. Women in TPTL with an antepartum hemorrhage were included in the study. Atypically, unless there is a massive antepartum hemorrhage of greater than 100 mL or symptoms of shock,¹² tocolysis is still considered in RFDS.¹³

If not contraindicated, cervical dilatation was assessed before the flight departure. This assessment, which was conducted via a speculum or vaginal examination, was attended either at the referring center or air side in the ambulance or aircraft by the attending flight nurse or medical officer. It is not standard RFDS practice to repeat vaginal examinations before departure or in flight unless clinically indicated.¹³ Women who were determined appropriate for inclusion (N = 236) were retrospectively divided into 2 intervention groups:

those who received nifedipine only and those who received salbutamol + nifedipine. Women who did not receive any tocolytics or were given salbutamol without nifedipine were excluded from the study.

Ethics approval was obtained from the Edith Cowan University Human Research Ethics Committee (ID: 2019-00793) and the RFDS Clinical Health Research Committee.

Tocolytic Therapy

The typical salbutamol regimen was 5 mg of the drug diluted in 100 mL normal saline administered at a rate of 12 mL/h; for nifedipine, the standard dose was 60 mg orally.

Tocolytic effectiveness was collated and coded from each case note as effective, partial, or not effective based on the following criteria:

1. Effective: contractions ceased on palpation.
2. Partial: on palpation, contractions reduced in strength and/or frequency but did not cease despite tocolysis.
3. Not effective: on palpation, no reduction in strength and/or frequency of contractions despite tocolysis.

Tocolytic effectiveness was ascertained by the flight nurse through intermittent abdominal palpation to determine whether contractions were successfully paused, completely halting labor.

RFDS clinical guidelines within WA advise to commence a trial of nifedipine for TPTL cases if the woman's cervix is less than 4 cm dilated unless contraindicated (eg, large antepartum hemorrhage, abruption, or fetal death). After this, if the labor persists after 90 minutes or if cervical dilatation is 4 cm or greater, rescue salbutamol tocolysis is to be started with the awareness of potential risks, including tachycardia, hypotension, tremor, pulmonary edema, hyperglycemia, and hypokalemia.¹³

Statistical Analysis

Data were analyzed using Excel (Microsoft, Redmond, WA) and the statistical software package R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Independent sample *t*-tests were used in the comparison of means between the groups, whereas the chi-square test with odds ratio analysis where appropriate was used in the comparison of proportions between groups. Statistical significance was determined at $P < .05$.

Results

Inclusion Criteria

During the study period between 2013 and 2018, there were 1,094 women who required an AR for pregnancy, including 405 (37.0%) for TPTL, by the RFDS within WA. To achieve a representative sample (95% confidence interval [CI]), we aimed to include a sample size of at least 197 TPTL patients.

To account for any potential missing clinical information, we included 324 women, equaling 80.0% of the TPTL total cohort. Each patient record was included in reverse chronological order until we achieved the desired representative sample size.

Of the 324 records, 63 retrievals were excluded for being obstetric retrievals not in TPTL (eg, ruptured membranes). A further 18 TPTL retrievals were excluded because the women did not require nifedipine therapy or salbutamol + nifedipine therapy. A further 7 women did not have enough recorded information to determine the course of events during retrieval. The total number of participants meeting the study inclusion criteria was 236, including 141 who received nifedipine and 95 receiving salbutamol + nifedipine (see Figure 1).

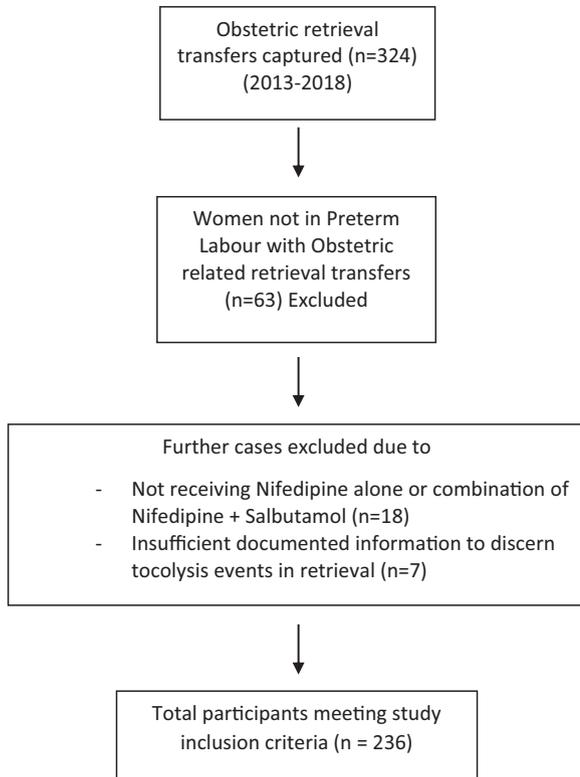


Figure 1. A flow diagram of participant selection.

Pregnancy Characteristics at Time of Retrieval

The mean age of the 236 women included in the study was 27.9 years (standard deviation = 6.1 years), with a significantly ($P < .05$) younger age in the salbutamol + nifedipine group (mean age = 26.9 years, SD = 5.5 years) compared with the nifedipine group (mean age = 28.7 years, SD = 6.4 years, $P < .05$) Table 1. demonstrates woman demographics and pregnancy characteristics. There were 88 women who identified as Aboriginal and/or Torres Strait Islander, with a significantly higher percentage ($P = .029$) of these women receiving salbutamol + nifedipine ($n = 44$, 46.3%) than nifedipine only ($n = 44$, 31.2%). The mean gestation during retrieval was 30.6 weeks (SD = 3.6 weeks), ranging from 30.5 weeks (SD = 3.9 weeks) in the salbutamol + nifedipine group to 30.8 weeks (SD = 3.3 weeks) in the nifedipine group.

Cervical dilatation ranged from cervical cerclage and closed to fully dilated (10.0 cm), with a mean cervical dilatation of 0.9 cm (SD = 1.5 cm) taken before transport. The salbutamol + nifedipine group had a significantly ($P < .05$) wider mean dilation of 1.4 cm (SD = 1.5 cm) compared with 0.5 cm (SD = 0.9 cm) in the nifedipine group.

There were 147 case notes reporting women who had at least 1 comorbidity, with nonsignificant ($P < .05$) differences between the groups (60 [63.2%] in the salbutamol + nifedipine group and 87 [61.7%] in the nifedipine group). The leading comorbidities included substance use disorders ($n = 31$, 21.1%), diabetes mellitus ($n = 16$, 10.9%), mental and/or behavioral disorders ($n = 12$, 8.2%), cardiovascular disease ($n = 12$, 8.2%), and cervical incompetence (also known as cervical weakness or insufficiency) ($n = 8$, 5.4%). The leading substance use disorders were tobacco smoking ($n = 9$, 29.0%), cannabis ($n = 9$, 21.95%), intravenous drug use ($n = 7$, 17.1%), and alcohol consumption ($n = 6$, 14.6%). There were no differences in proportions of substance use disorders between the salbutamol + nifedipine group ($n = 17$, 11.5%) compared with the nifedipine group ($n = 14$, 9.5%).

Flight Characteristics

The priority of the AR is determined by the medical officer who receives the air medical tasking. It is dependent on the clinical condition of the laboring woman, their location, and the obstetric support available. There were 7 (3.0%) priority 1 transfers requiring immediate retrieval, 204 (86.4%) priority 2 transfers requiring urgent medical retrieval, and 25 (10.6%) priority 3 less urgent medical transfers.¹⁴ A higher mean severity score was evident in the salbutamol + nifedipine group (priority 1 = 6.3%, priority 2 = 90.5%, and priority 3 = 3.15%) versus the nifedipine group (priority 1 = 0.7%, priority 2 = 83.7%, and priority 3 = 15.6%). The salbutamol + nifedipine group was more likely ($P = .003$; odds ratio [OR] = 2.2; 95% CI, 1.31–3.81) to have both a flight nurse and a medical officer ($n = 56$, 59.6%) compared with the nifedipine group ($n = 56$, 39.7%). There were no differences in cabin altitude, ambient altitude, or the time traveled between salbutamol + nifedipine tocolysis versus nifedipine-only tocolysis transfers.

Tocolytic Effectiveness and Side Effects

Of the total of 236 women included in this study, there were 151 cases of tocolytic effectiveness. Effective tocolysis was significantly more likely (OR = 1.76; 95% CI, 1.01–3.07; $P = .046$) in the salbutamol + nifedipine group (68/95 effective, 71.6%) compared with the nifedipine group (83/141 effective, 58.9%). The salbutamol + nifedipine group was more likely to suffer from maternal tachycardia ($n = 87$ [91.6%] vs. $n = 62$ [44.0%]; OR = 13.86; 95% CI, 6.25–30.74; $P < .001$), fetal tachycardia ($n = 26$ [27.4%] vs. $n = 13$ [9.2%]; OR = 13.86; 95% CI, 6.25–30.74; $P < .001$), nausea ($n = 17$ [17.9%] vs. $n = 5$ [3.55%]; OR = 5.93; 95% CI, 2.11–16.69; $P < .001$), and vomiting ($n = 12$ [12.6%] vs. $n = 2$ [1.4%]; OR = 10.05; 95% CI, 2.19–46.01; $P < .001$). Of these, 3 women developed significant side effects after salbutamol. These included 2 women who suffered cardiac effects of chest pain with associated electrocardiographic changes (case A: ST depression lead I, II, and III and Augmented Vector Foot (AVF) and ST-elevation Augmented Vector Right (AVR); case B: flat lead II, III, and ST depression V4–V6) despite no previous cardiac history. The third woman developed severe metabolic and lactic acidosis, which was managed in flight. The results confirmed a woman developing severe complications after salbutamol + nifedipine therapy was less than 2% (1.18%) compared with no cases in the nifedipine group.

Antepartum Hemorrhages and Threatened Preterm Labor

Twenty cases (8.47%) reviewed had a small amount of bleeding and were not contraindicated to receive tocolytic therapy because transport to higher medical care was prioritized. Twelve of these women were given nifedipine + salbutamol, and 8 received nifedipine only. Gestation ranged from 22 + 6 weeks to 33 + 4 weeks. Cervical dilatation ranged from closed to fully dilated during transfer. All but 2 cases were effectively tocolyzed. Of the 2 women who continued to labor in flight, the first flight was a duration of 1 hour 5 minutes; nifedipine was ineffective, and salbutamol was not commenced. The woman started involuntarily pushing on landing in Perth, was assessed to be fully dilated, and continued en route to a tertiary hospital via a priority 1 road ambulance. The second woman received nifedipine and then salbutamol, which caused significant maternal tachycardia and was ceased accordingly. Contractions continued regularly in flight, again a short flight duration of 28 minutes within the southwest region of WA. Women in TPTL diagnosed with an antepartum hemorrhage typically suffered from tachycardia and tachypnea after tocolysis in flight. These symptoms did not cause further clinical distress or deterioration.

Table 1
Preterm Labor Maternal Characteristics and Effectiveness of Salbutamol and Nifedipine Compared With Nifedipine-Only Therapy

Description	Total Population	Salbutamol + Nifedipine	Nifedipine Only
Total preterm labor population (%)	236	95 (40.2)	141 (59.75)
Mother characteristics			
Mean age in years (SD)	27.89 (6.081)	26.91 (5.51)	28.67 (6.41) ^a
Mean weight in kg (SD)	75.92 (16.506)	76.49 (18.93)	75.81 (15.21)
Number Indigenous (%)	88 (37.3)	44 (46.3) ^a	44 (31.2)
Number non-Indigenous (%)	136 (57.6)	48 (50.5)	88 (62.4)
Missing Indigenous status (%)	12 (5.1)	3 (3.2)	9 (6.4)
Drug and alcohol use during current pregnancy (%)	41 (17.4)	24 (25.3) ^a	17 (12.1)
At least 1 comorbidity at retrieval (%)	147 (62.3)	60 (63.2)	87 (61.7)
Pregnancy characteristics			
Mean gestation in weeks (SD)	30.58 (3.626)	30.53 (3.92)	30.84 (3.34)
Mean parity (SD)	1.58 (1.644)	1.53 (1.45)	1.63 (1.64)
Mean gravida (SD)	3.15 (2.034)	3.13 (1.97)	3.27 (2.07)
Mean initial assessment of cervical dilatation in cm (SD)	0.9 (1.457)	1.40 (1.51) ^a	0.48 (0.93)
Flight characteristics			
Tasking priority 1 (%)	7 (3.0)	6 (6.3)	1 (0.7)
Tasking priority 2 (%)	204 (86.4)	86 (90.5)	118 (83.7)
Tasking priority 3 (%)	25 (10.6)	3 (3.2)	22 (15.6)
Number of FNs (%)	123 (52.1)	38 (40.0)	85 (60.3) ^a
Number of MOs (%)	1 (0.4)	1 (1.5)	0 (0.0)
Number of FNs + MOs (%)	112 (47.4)	56 (59.6%)	56 (39.7%)
Maximum cabin altitude in feet (SD)	5,474.01 (2,117.25)	5,786 (1,802)	5,301 (2,275)
Maximum ambient altitude in feet (SD)	20,452.08 (5,538.454)	20,955 (4,762)	20,107 (5,920)
Tocolytic effectiveness			
Number not effective: on palpation, no reduction in strength and/or frequency of contractions despite tocolysis (%)	25 (10.6)	11 (11.6)	14 (9.9)
Number partially effective: on palpation, contractions reduced in strength and/or frequency but did not cease despite tocolysis. (%)	60 (25.4)	16 (16.8)	44 (31.2)
Number effective: contractions ceased on palpation (%)	151 (64.0)	68 (71.6) ^a	83 (58.9)
Tocolytic side effects (%)			
Maternal tachycardia	149 (63.1)	87 (91.6) ^b	62 (44.0)
Fetal tachycardia	39 (16.5)	26 (27.4) ^b	13 (9.2)
Hypotension	17 (7.2)	9 (9.5)	8 (5.7)
Nausea	22 (9.3)	17 (17.9) ^b	5 (3.55)
Vomiting	14 (5.9)	12 (12.6) ^b	2 (1.4)
Chest pain	2 (0.8)	2 (0.8)	0 (0.0)
Metabolic acidosis	1 (0.4)	1 (0.4)	0 (0.0)

FNs = flight nurses; MOs = medical officers; SD = standard deviation.

^a $P < .05$.^b $P < .001$.

Discussion

Despite tocolysis occurring at various times in the first stage of labor with progressing labors and unsuccessful nifedipine tocolysis, rescue tocolysis with salbutamol proved efficacious. As per other air medical research,^{1,15,16} we found that no preterm births occurred in flight using salbutamol + nifedipine rescue tocolysis. Unlike Akl and colleagues¹⁵ who reported no significant complications with salbutamol tocolysis, our study uncovered 3 women who developed marked side effects after salbutamol use. This difference could be due to the women in Akl et al's study¹⁵ indicating that recently retrieved women have higher rates of reported chronic disease and pregnancy risk factors.^{1,17}

The results of our study identified that severe complications after salbutamol + nifedipine therapy were rare. These findings are essential in the prevention of remote preterm births for practitioners who are not currently using salbutamol tocolysis for the treatment and management of TPTL. Martin et al¹⁸ undertook a study over a 3-year period in the Northern Territory of Australia; they reported nifedipine-only tocolysis resulted in only 3 in-flight births out of a total sample size including 304 cases. The significant differences of in-flight birth rates reported by Martin et al,¹⁸ the same as were found in our study, indicate rescue salbutamol should be considered for the management and treatment of TPTL in remote locations across Australia and arguably globally with the urgent need to standardize TPTL practice management.

Because of the potential for adverse implications in women with existing heart disease, namely rheumatic heart disease (RHD), which is noted to be common in remote Australia,¹⁹ practitioners may be reluctant to use beta-agonists. Unfortunately, our research did not verify safety for women with RHD because only 2 women were reported to suffer from RHD, and neither required salbutamol tocolysis. Another 2 women suffered from heart disease; 1 did not receive salbutamol, and the other developed severe complications of metabolic acidosis. RFDS clinical guidelines encourage caution with cardiovascular disease and salbutamol use.²⁰ Despite no available research on salbutamol use with women who suffer from heart disease who are in TPTL, 1 study (the BALTI-2 [Beta-Agonist Lung Injury Trial-2] study) demonstrated beta-agonist use in critical illness can potentially exacerbate myocardial injury and cardiac failure.²¹ The study was ceased midtrial in the treatment of acute respiratory distress syndrome with a 7-day continuous infusion of salbutamol due to a significant rise in mortality. This is as close as a comparison available for beta-agonist use in the emergency retrieval setting where infusions last from 30 minutes up to 12 hours on average in WA. As discussed previously, the findings from the BALTI-2 study are alarming and indicate the need for further research in the air medical use of salbutamol tocolysis in women with TPTL and cardiovascular disease.²¹

In our study, the incidence of metabolic changes secondary to salbutamol was scarce. Two cases demonstrated women who suffered

hypokalaemia requiring supplementation, and a further 2 were diagnosed with hyperglycaemia. Routine blood glucose and potassium levels were not checked each flight; therefore, it is anticipated that further metabolic changes may have been found with greater blood analysis in flight. Many variables, including infusion duration, were outside the scope of this research. These variables warrant additional research to ascertain the safest, yet most effective dosage, minimizing side effects in tocolysis for the treatment of TPTL in flight.

Women who identified as Aboriginal and Torres Strait Islander had higher comorbidities and higher modifiable risk factors, including alcohol and tobacco consumption during pregnancy, and were more likely to progress to needing salbutamol + nifedipine tocolysis. These findings suggest a link between comorbidities; drug and alcohol use; and progressive, resistant TPTL in the Aboriginal and Torres Strait Islander population. This knowledge can be used for air medical clinicians to anticipate the need for more aggressive tocolysis if the woman in TPTL has comorbidities, partakes in drug or alcohol use, or is of Aboriginal or Torres Strait Islander descent.

Our findings also determined women who received salbutamol + nifedipine were more likely to have a higher severity, which resulted in a flight nurse and a medical officer being tasked rather than a solo flight nurse. The higher priority and multicrew tasking with salbutamol + nifedipine shows it is more likely to be used in complex progressing TPTL cases in which aggressive tocolysis is required under judicious advanced care to ensure maternal and fetal safety is maintained while achieving in utero air medical transfer.

Women most likely to benefit from the use of a tocolytic drug are those who are very preterm or women who have not yet completed a full course of corticosteroids. The National Institute of Clinical Excellence stated that tocolytic therapy is contraindicated in placental abruption and is “relatively contraindicated” in “mild hemorrhage” due to placenta previa.¹² Our study reviewed 20 women who were tocolyzed with small antepartum bleeds associated with TPTL. The common side effects found were tachycardia and tachypnea. No further clinical deterioration occurred after these side effects. Our research supports tocolysis use when TPTL is associated with a small antepartum hemorrhage with successful tocolysis and manageable side effects. For extremely premature born neonates, 20% have a maternal diagnosis of TPTL and Antepartum Haemorrhage (APH).¹² In addition to this, there is a known correlation between extreme prematurity, APH, and cerebral palsy.¹² Our study demonstrates women with a small APH in TPTL can be safely tocolyzed to facilitate expectant birth care. This may also include the use of corticosteroids, which has been proven to reduce rates of cerebral palsy and morbidity in extreme premature neonates.^{4,6}

There were a number of limitations in this study. We did not collect patient hospital outcomes, such as gestational age at birth, mode of birth, special care nursery admission, birth weight, resuscitation, and stillbirth rates. Further research is required to identify the impact of tocolysis postretrieval when the woman reaches definitive care. Furthermore, we analyzed a subset of RFDS data collected between 2013 and 2018, meaning the data were not exhaustive of all cases between this period.

Conclusion

Our findings demonstrate rescue salbutamol tocolysis to be efficacious. Women residing in remote locations in TPTL are at risk of preterm birth and must be considered suitable candidates in receiving

rescue salbutamol. Acknowledgment and caution must be given with temporary side effects of maternal nausea, vomiting, and maternal and fetal tachycardia possible. A reduction in remote preterm birth rates and improved neonatal outcomes could potentially be achieved using the RFDS salbutamol tocolytic regimen for air medical TPTL transfers. These findings are transferrable in AR services where pregnant women are flown over large distances.

Additional in-flight research is needed to determine the effects for women with pre-existing cardiac disease receiving salbutamol tocolysis. Maternal and neonatal outcomes could be improved with aggressive salbutamol tocolysis throughout the Northern Territory of Australia if proven to be safe to use in women with RHD. Similarly, postpartum outcomes secondary to in-flight TPTL tocolysis would be invaluable, particularly in pertaining to hemorrhage and infection rates.

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