Received: 9 July 2022 | Accepted: 4 November 2022

DOI: 10.1111/dme.15003

DIABETIC Medicine

LETTER

Adoption of a pregnancy-specific intravenous insulin protocol (Pregnancy-IVI) at a regional centre has equivalent safety and efficacy outcomes as a tertiary hospital

Women with diabetes in pregnancy (DIP) are at risk of hyperglycaemia during hospitalisation for administration of antenatal glucocorticoids, intercurrent illness and labour. Variable rate intravenous insulin (VRII) is commonly used to maintain maternal glucose at physiological levels, to minimise maternal ketoacidosis, fetal acidosis and neonatal hypoglycaemia.[1,2] The Pregnancy-IVI is the most-studied VRII protocol, and has established efficacy and safety following betamethasone in gestational diabetes mellitus[2] and pre-existing[3] diabetes mellitus. However, implementation has only been reported at tertiary care hospitals, and it is unclear whether VRII can be safely implemented in secondary care hospitals in regional areas, particularly with reference to the risk of maternal hypoglycaemia.[4,5]

Real-world safety and efficacy data for performance of the Pregnancy-IVI VRII at a regional obstetric hospital in Australia are presented and compared to outcomes at its tertiary-referral hospital.

A retrospective cohort study enrolled all women with DIP at a regional centre and a tertiary centre receiving Pregnancy-IVI for glycaemic instability following betamethasone ($n = 202$), intercurrent illness ($n = 45$) or labour ($n = 167$) during 2020–2021. The Pregnancy-IVI VRII is standard of care at these institutions for management of unstable glucose in hospitalised women with DIP, and is publicly available.[2,3] Pregnancy-IVI is administered on general maternity wards by midwives, supervised by obstetricians, with identical midwife: patient ratios (1:6). At the tertiary hospital, a higher volume of DIP is managed, with on-site endocrinology consultation available. Data were systematically extracted using a standardised template. Type 1 diabetes mellitus cases were excluded (guidelines required universal tertiary care). The primary efficacy endpoint was on-IVI maternal glycaemic time-in-range (4.0–7.8 mmol/L). The safety endpoint was duration of on-IVI maternal hypoglycaemia at a 3.8 mmol/L or <3.0 mmol/L threshold, reported as hours per 100 woman-IVI-hours (h/100 wh). Capillary glucose was measured every 30–60 min during IVI. Outcomes were assessed using Mann–Whitney or 95% CI of risk difference, stratified by indication for Pregnancy-IVI. The study was approved by the IRB, waiving the requirement for consent as this was a study of practice.

In all, 411 women, cared for at a tertiary ($n = 344$) or regional ($n = 67$) hospital, were included and had similar characteristics (Table 1). Gestational diabetes mellitus was diagnosed in 87%. Indication for IVI, and duration of infusion, was similar between sites. The primary efficacy outcome (maternal on-IVI time in range) was similar across sites (tertiary vs. regional) for all indications: 82.4% vs 76.7% for betamethasone ($p = 0.060$), 90.0% vs 93.8% for labour ($p = 0.529$) and 86.8% vs 87.0% for illness ($p = 0.658$). The safety outcome (duration of maternal hypoglycaemia) was also similar across sites (tertiary vs. regional) at the 3.8 mmol/L threshold: 0.5 h vs 0.6 h/100 wh following betamethasone ($p = 0.410$), 1.6 h vs 0.6 h/100 wh during labour ($p = 0.094$), 0.7 h vs 1.4 h/100 wh during illness ($p = 0.126$). At the 3.0 mmol/L threshold, maternal hypoglycaemia was uncommon (0.0–0.3 h/100 wh) and did not differ by indication or site ($p > 0.05$ for all, Table 1).

These data demonstrate the safe and effective implementation of protocolised glycaemic care for DIP through use of a midwife-delivered, ward-based Pregnancy-IVI VRII algorithm. While the Pregnancy-IVI is effective and safe in a high-volume tertiary centre (14.3 infusions/month), the demonstration of equivalent implementation outcomes in a lower volume centre (2.8 infusions/month) provides important reassurance of the generalisability of this VRII. In particular, the absence of any trend towards increased maternal hypoglycaemic risk at the regional hospital is reassuring, as is the extremely low rate of significant maternal hypoglycaemia across both sites.

These data address theoretical concerns raised in recent Joint British Diabetes Societies guidelines[4] regarding safe implementation of VRII outside specialised tertiary units.

TABLE 1 Demographic and outcome data of Pregnancy-IVI, stratified by site of implementation

	Tertiary hospital	Regional hospital	*p*-value
Patient demographics			
n	344	67	
Age (years)	32.1 ± 5.3	32.1 ± 5.7	0.923
Gravida	2 (1–4)	3 (1–4)	0.797
Para	1 (0–2)	1 (0–2)	0.814
Tobacco use (*n*)	47/344 (14%)	9/67 (13%)	0.946
BMI (kg/m^2)	32.6 ± 8.6	33.3 ± 6.6	0.494
Gestational age at IVI (weeks)	36.2 (32.3–38.0)	36.8 (34.6–38.0)	0.242
Diabetes type			0.595
Gestational	300 (87%)	60 (90%)	
Type 2	44 (13%)	7 (10%)	
Duration of IVI (hrs)			
Overall	20.0 (6.5–39.5)	19.0 (6.5–34.5)	0.634
Betamethasone	38.5 (30.0–43.5)	32.8 (21.5–42.0)	0.212
Labour	5.5 (3.5–8.5)	7.0 (3.5–12.0)	0.241
Illness	22.0 (17.5–30.5)	24.3 (14.5–39.5)	0.941
Indication for IVI			
Betamethasone	176 (50.6%)	26 (38.8%)	0.900
Labour	140 (40.7%)	27 (40.3%)	
Illness	31 (9.0%)	14 (20.9%)	
% on-IVI Time in range 4.0–7.8 mmol/L			
Betamethasone	82.4 (74.5–89.7)	76.7 (68.4–86.1)	0.060
Labour	90.0 (73.2–100.0)	93.8 (80.0–100.0)	0.529
Illness	86.8 (76.5–94.3)	87.0 (64.2–94.3)	0.658
Maternal hypoglycaemia			95% CI of risk difference, *p*-value
Hours with glucose <3.8 mmol/L per 100 woman IVI hours			
Betamethasone	0.5	0.6	−0.5 to 0.2 $p = 0.410$
Labour	1.6	0.6	0.1 to 1.9 $p = 0.094$
Illness	0.7	1.4	−1.6 to 0.3, $p = 0.126$
Hours with glucose <3.0 mmol/L per 100 woman IVI hours			
Betamethasone	0.1	0.0	0.0 to 0.1 $p = 0.460$
Labour	0.1	0.0	0.0 to 0.3 $p = 0.632$
Illness	0.1	0.3	−0.6 to 0.3 $p = 0.468$

Note: Data are mean (*SD*), median (IQR) or *n* (%). *p*-value is for comparison between tertiary vs. regional hospital (excluding Type 1 diabetes).
Abbreviations: BMI, Body Mass Index; IVI, Intravenous Insulin; *n*, Number of women.

While appropriate staff training and careful implementation of VRII is essential irrespective of setting, these data demonstrate that on-site endocrinology support is not necessarily a pre-requisite for effective VRII implementation, and that VRII can be safely administered in a ward-setting by midwives on a less frequent basis, with appropriate obstetric supervision and as-needed remote endocrine consultation.

A key strength of this study is the evaluation of 'real-life' routine practice, rather than of the rigorous environment of a prospective trial. It is important to emphasise that this study was not conducted after a specific period of intensive staff training at either site; the Pregnancy-IVI protocol has been in routine use since 2017 (tertiary) and 2019 (regional), supported by ad-hoc ward-based education. Furthermore, the inclusion of a 24-month period necessarily includes several periods of new staff induction and staff turnover, as commonly occurs in clinical environments.

A potential limitation of this study is that more complex patients may be cared for at the tertiary centre, which could bias glycaemic endpoints. However, there was no significant difference in maternal age, body mass index, type of diabetes or in gestational age at IVI administration to suggest a true difference in the comparator populations (Table 1). Furthermore, the tertiary hospital is also the primary obstetric hospital for a large urban catchment, so the majority of women with DIP at both centres are representative of the region.

In conclusion, these data support the safe and effective implementation of the Pregnancy-IVI VRII protocol in women with gestational and type 2 diabetes admitted to a regional obstetric centre.

ACKNOWLEDGEMENT

Open access publishing facilitated by The University of Newcastle, as part of the Wiley - The University of Newcastle agreement via the Council of Australian University Librarians.

Christopher W. Rowe[1,2]
Vivian Qiao[2]
Soundarya Ramesh[2]
Patrick Rosee[2]
Angeline Sathiakumar[2]
Sienna McWhae-Brown[3]
Eliza Griffiths[2,3]
Katie Wynne[1,2]

[1]*Department of Diabetes and Endocrinology, John Hunter Hospital, Newcastle, Australia*
[2]*School of Medicine and Public Health, University of Newcastle, Callaghan, Australia*
[3]*Department of Maternity and Gynaecology, The Maitland Hospital, Maitland, Australia*

Correspondence
Christopher W. Rowe, Department of Diabetes and Endocrinology, John Hunter Hospital, Newcastle, Australia.
Email: christopher.rowe@health.nsw.gov.au

ORCID

Christopher W. Rowe https://orcid.org/0000-0002-9652-6562

REFERENCES

1. Dashora U, Temple R, Murphy H. Management of Glycaemic control In pregnant women with diabetes on obstetric wards and delivery units. *Joint British Diabetes Society for Inpatient Care*; 2017. http://www.diabetologists-abcd.org.uk/JBDS/JBDS_Pregnancy_201017.pdf. Accessed June 3, 2022.
2. Rowe CW, Putt E, Brentnall O, et al. An intravenous insulin protocol designed for pregnancy reduces neonatal hypoglycaemia following betamethasone administration in women with gestational diabetes. *Diabet Med*. 2018;36(2):228-236. doi:10.1111/dme.13864
3. Rowe CW, Watkins B, Brown K, et al. Efficacy and safety of the pregnancy-IVI, an intravenous insulin protocol for pregnancy, following antenatal betamethasone in type 1 and type 2 diabetes. *Diabet Med*. 2020;38(4):e14489. doi:10.1111/dme.14489
4. Dashora U, Levy N, Dhatariya K, Willer N, Castro E, Murphy H. Managing hyperglycaemia during antenatal steroid administration, labour and birth in pregnant women with diabetes – an updated guideline from the joint British diabetes Society for Inpatient Care. *Diabet Med*. 2021;39(2):e14744. doi:10.1111/dme.14744
5. Rowe CW, Wynne K. Re: managing hyperglycaemia during antenatal steroid administration, labour and birth in pregnant women with diabetes – an updated guideline from the joint British diabetes Society for Inpatient Care. *Diabet Med*. 2022;39:e14848. doi:10.1111/dme.14848