Institution: University of East Anglia

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Improving Neonatal Health Outcomes using Continuous Glucose Monitoring in Pregnant Women with Type 1 Diabetes (CONCEPTT)

Period when the underpinning research was undertaken: 2013 to 2019

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Helen Murphy	Clinical Professor in Medicine	2015 to present

Period when the claimed impact occurred: 2018 to 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Research into Continuous Glucose Monitoring (CGM) conducted at the University of East Anglia (UEA) has led to a fundamental change in the care of pregnant women with type 1 diabetes, in the UK and internationally. A UEA led multinational trial (CONCEPTT) demonstrated that use of CGM improved maternal glucose levels and led to significant improvements in neonatal health outcomes. In consequence, CGM is now recommended as first line therapy for the management of type 1 diabetes pregnancy in the UK, and has been incorporated into NICE Guidelines with accelerated NHS implementation. On top of the health outcomes, NHS cost savings in excess of GBP9,000,000 are estimated annually.

2. Underpinning research

Diabetes is the most common medical condition in pregnancy, affecting one in ten pregnant women. Type 1 diabetes, where the pancreas cannot produce insulin to regulate glucose levels, is the most serious condition. Annually, type 1 diabetes adversely impacts 2,000 pregnant women and babies in England and Wales alone.

Serious complications, such as birth defects, stillbirth and newborn death, occur in 1 in 12 of those pregnancies. Furthermore, one in two babies suffer from complications of preterm birth and large birthweight, often with severe consequences for the woman and her infant, and additional resource burden for the NHS. The importance of self-monitoring of blood sugars for maintaining optimal glucose levels during pregnancy has been known about for the past 50 years. A sensor-based method called Continuous Glucose Monitoring (CGM) was available, but expensive relative to existing fingerstick glucose monitoring. Moreover, the impact of sustained use of CGM on longer-term health outcomes was unclear, as were the risks and benefits of its use during pregnancy.

Professor HR Murphy (at UEA from 2015) and Prof Denice Feig (Toronto) jointly led the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy (CONCEPTT) Trial that was conceived to fill that knowledge gap. Conducted between 2013 and 2017, it was based on a small sensor (the size of a two-pound coin) inserted beneath the skin which continuously measured glucose levels, and wirelessly sent a continuous stream of glucose data to a mobile phone or insulin pump device.

The trial, supported by the Centre for Mother, Infant, and Child Research (Toronto, Canada) and Jaeb Center For Health Research (Tampa, USA), established 31 collaborative centres throughout the UK, Canada, Italy, Spain, Ireland and the USA. The study recruited and randomized 325 women with type 1 diabetes. To date, eight full manuscripts have been published (12 publications in total) with eight sub-studies and ongoing contributions to national and international clinical guidelines.

The results of the trial demonstrated that pregnant women using CGM had improved glucose levels, spending on average, an additional 1.7 hours per day in the target glucose range (1). A higher proportion of CGM users achieved the NICE recommended glucose control target measured by HbA1c (66% vs. 52%; CGM vs control). Importantly, birth outcomes improved for newborns whose mothers used CGM, reducing the number of babies born overweight or obese

(53% vs 69%), reducing the number of newborns admitted for neonatal intensive care (27% vs 43%), and reducing the number of newborns with dangerously low glucose levels after birth (15% vs 28%). Babies whose mothers used CGM also left hospital one day earlier (3 vs 4 days; CGM vs SMBG). These data were consistent across international sites, maternal dietary intakes and methods of insulin delivery (2, 3). They defined the benefits of CGM use in type 1 diabetes pregnancy, demonstrating that CGM use reduced newborn hypoglycaemia by improving maternal glucose levels during the second and third trimesters of pregnancy (4).

CGM use was highly cost effective from a neonatal perspective (minus GBP1,570/QALY) with health economic analyses demonstrating consistent cost savings of approximately 30% across international health care settings (5).

Based on our findings, time spent in the target glucose range (CGM time-in-range) is now internationally accepted as a clinically meaningful marker for glucose control in pregnancy, as a primary outcome measure for clinical trials and widely endorsed by patients and healthcare providers for making clinical decisions and adjusting diabetes treatment regimens.

3. References to the research

1. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial
   Feig, D.S., Donovan, L.E., Corcoy, R., Murphy, K.E., Amiel, S.A., Hunt, K.F., Asztalos, E., Barrett, J.F.R., Sanchez, J.J., de Leiva, A., Hod, M., Jovanovic, L., Keely, E., McManus, R., Hutton, E.K., Meek, C.L., Stewart, Z.A., Wysocki, T., O'Brien, R., Ruedy, K., Kollman, C., Tomlinson, G., **Murphy, H.R**. CONCEPTT Collaborative Group.
   The Lancet, **2017**, 390(10110), 2347-2359.
   DOI: 10.1016/S0140-6736(17)32400-5
2. Pumps or Multiple Daily Injections in Pregnancy Involving Type 1 Diabetes: A Prespecified Analysis of the CONCEPTT Randomized Trial
   Feig, D.S., Corcoy, R., Donovan, L.E., Murphy, K.E., Barrett, J.F.R., Sanchez, J.J., Wysocki, T., Ruedy, K., Kollman, C., Tomlinson, G., **Murphy, H.R.** CONCEPTT Collaborative Group.
   Diabetes Care, **2018**, 41(12), 2471-2479. DOI: 10.2337/dc18-1437.
3. Dietary intakes of women with Type 1 diabetes before and during pregnancy: a pre-specified secondary subgroup analysis among CONCEPTT participants
   Neoh, S.L., Grisoni, J.A., Feig, D.S., **Murphy, H.R.** CONCEPTT Collaborative Group.
   Diabetic Medicine, **2019**, 37(11), 1841-1848. DOI: 10.1111/dme.13937
4. Continuous Glucose Monitoring in Pregnant women with Type 1 Diabetes. Cost-effective analyses of the CONCEPTT randomized controlled trial
   Murphy, H.R, Feig, D.S., Patel, N.
   American Diabetes Association: Oral Presentation, **2019** Jun; 68(Supplement 1).
   DOI: 10.2337/db19-351-OR
5. Modelling potential cost savings from use of real-time continuous glucose monitoring in pregnant women with Type 1 diabetes
   Murphy, H.R, Feig, D.S, Sanchez, J.J, de Portu, S., Sale, A. CONCEPTT Collaborative Group
   Diabetic Medicine, **2019**, 36(12), 1652-1658. DOI: 10.1111/dme.14046

Grant Information

i) **New Technologies to improve glucose control and infant outcomes in pregnant women with type 1 diabetes.** (PI) Murphy, H.R.
Funder: National Institute for Health Research, Career Development Fellowship.
Dates: 01/11/2013 to 31/10/2016. Grant value: GBP810,310 (UEA GBP357,252)

4. Details of the impact

The results of the UEA led CONCEPTT trial, published in 2017, have been translated into new national and international policy and practice that are having positive impacts on the care of pregnant women with type 1 diabetes, delivering substantial health benefits for those mothers and their babies. In the UK, the NHS anticipates significant cost savings, with reduced pressure on

antenatal services, maternity wards, and neonatal intensive care units as well as improved patient experiences.

Changes to National Policy and Guidelines
The NHS accelerated CGM implementation pathway [A, B, C]
Based on the CONCEPTT results, National Health Service England (NHSE) have, in their Long Term Plan [Source A (i)], incorporated an accelerated implementation pathway, with funding for CGM (GBP2,000 per pregnancy) allocated to local maternity services starting from 01 November 2020. Local maternity services must now make CGM available to all pregnant women with type 1 diabetes by March 2021:

> *"...all pregnant women with type 1 diabetes will be offered continuous glucose monitoring, helping to improve neonatal outcomes."* [Source A (ii) page139]

Among pregnant women with diabetes, the risks of infection and of stillbirth are influenced by the quality of glucose control. CGM improves maternal glucose levels during pregnancy and because live CGM data are remotely shared with healthcare providers, CGM assists patients and healthcare providers in adjusting diabetes treatment during virtual appointments, which is particularly important for safely managing pregnant women during the COVID19 pandemic. The LTP FAQs clearly set out the neonatal health benefits citing the CONCEPTT findings. [Source A (iii) page151]

Similar changes to healthcare policy with ring-fenced CGM funding for all pregnant women with type 1 diabetes to be offered CGM have been introduced in Wales [B] and in Scotland [Source C]. A Technology Evidence Appraisal from NHS Wales reported that CGM use improves glycaemic control and reduces the incidence of pre-eclampsia in the mother, and reduces neonatal hypoglycaemia and the need and duration of neonatal intensive care stay for the baby [Source B (ii)]. NHS Trusts in England and Wales must now adopt this guidance [Sources A, B].

Equality and health inequalities impact assessments to ensure widespread digital inclusion for equitable implementation of CGM for all pregnant women with type 1 diabetes are now underway across all NHS regional maternity networks [Source A (iii)].

Changes to NICE Guidelines [D]
In the wake of the publication of the CONCEPTT findings, multiple professional and patient organisations called for a review of NICE Guidelines. These included the Royal College of Obstetricians and Gynaecologists; the Royal College of Physicians and Surgeons of Glasgow; the Association of British Clinical Diabetologist; the Diabetes Technology Network; Diabetes UK, the Juvenile Diabetes Research Foundation (JDRF) and INPUT Patient Advocacy. NICE issued the following statement:

> *"There is new evidence on continuous glucose monitoring. In particular, the CONCEPTT trial has published which experts deem to be a landmark trial that provides the best available evidence for the foreseeable future. The CONCEPTT trial found improvements in a range of neonatal outcomes with continuous glucose monitoring… and advocates routine usage in pregnant women with type 1 diabetes."* [Source D(i)]

The NICE guideline review, published December 2020 [Source D (iii)], states that, based on high quality randomised controlled trial data (taken from the CONCEPTT trial), continuous glucose monitoring (CGM) resulted in

- More pregnant women achieving the blood glucose targets
- Fewer caesarean sections
- Fewer neonatal intensive care unit (NICU) admissions

The current NICE guideline now states:

> "*Offer continuous glucose monitoring (CGM) to all pregnant women with type 1 diabetes to help them meet their pregnancy blood glucose targets and improve neonatal outcomes."* [Source D (ii)]

Patient organisations [E]
These national policy and guideline changes are strongly endorsed by patient organisations including Diabetes UK, who issued a Position Statement recommending that, for pregnant women,

"*real-time CGM with alarms should be considered as first-line therapy*" [Source E (i)] and the Juvenile Diabetes Research Foundation (JDRF) who stated that:

> "*The provision of CGM will help keep mothers and their babies healthy, and will help set world standards for the provision of medical technology for pregnant women with type 1 diabetes."* [Source E (ii)]

Cost and Other Resource Benefits to the NHS [B, F]
Initial cost modelling estimates by NHS Wales point to immediate savings of GBP1,029 per pregnancy from the reduction in neonatal intensive care requirements [Source B (i)]. A budget impact model (conducted by the CONCEPTT team and CGM device manufacturers) has estimated that the annual saving to the NHS from managing type 1 diabetes pregnancy using CGM will be in the region of GBP9,500,000 annually (with current costs running at close to GBP24,000,000, and those post implementation at just over GBP14,000,000) [Source F].

Driving Change in Policy and Practice Overseas [G, H, I, J]
Based on the CONCEPTT results, because of the low use of CGM prior to 2019, time-in-range glucose targets for CGM use are being introduced into clinical research and into policy and practice frameworks for managing diabetes during pregnancy internationally [Source G (i)]. CGM time-in-range is the only glucose outcome measure that both reflects patients' priorities and can be used to quantitatively evaluate treatment efficacy.

Furthermore, research funders now recognize CGM time-in-range as a primary outcome measure in national and international type 1 diabetes pregnancy clinical trials [Source G (ii)].

In **the USA**, CGM use in type 1 diabetes pregnancy has increased from 17% to 36% [Source H (i)], and was endorsed by the 2020 American Diabetes Association (ADA) standards of care, which stated that CGM can help achieve glucose control targets, reduce macrosomia (excessive birth weight) and neonatal hypoglycaemia [Source H (ii)].

In **Australia**, eligibility for fully subsidised continuous glucose monitoring was expanded under the National Diabetes Services Scheme in 2019 to include: women with type 1 diabetes who are pregnant, breastfeeding or actively planning pregnancy. On 1st March 2019, the Hon. Greg Hunt, Minister of Health, stated:

> *"Funding over the next five years will assist 37,000 eligible Australians with type 1 diabetes through the expansion of the Continuous Glucose Monitoring (CGM) Initiative."* [Source I]

Likewise, in **Sweden**, the use of CGM is now reimbursed both before pregnancy and as part of routine antenatal care:

> *"In Sweden, the use of CGM is reimbursed in type 1 diabetes outside of pregnancy if adequate glucose control is not achieved by conventional methods, and for all women in pregnancy."* [Source J]

5. Sources to corroborate the impact

A) i) The NHS Long Term Plan, NHS, 2019, Diabetes 3.80, page 65
ii) NHSE CGM Letter
iii) CGM in pregnancy with Type 1 Diabetes – FAQs

B) i) Health Technology Wales (HTW) Guidance 012 (September 2019): Continuous glucose monitoring in pregnant women with type 1 diabetes, p. 1
ii) Health Technology Wales Evidence Appraisal Report, p. 5, para 6.1.1, and 6.1.2 and references (R1) in Table 3 pp. 9 – 10.

C) Scottish Health Technology Group (SHTG) Adaption. (November 2020): Continuous glucose monitoring in pregnant women with type 1 diabetes, page 1.

D) i) NICE Surveillance Report, Surveillance of diabetes in pregnancy: management from preconception to the postnatal period (NICE guideline NG3), **2018**, page 3, para 1.3

ii) NICE Guideline, Diabetes in pregnancy: management from preconception to the postnatal period, **2015 (updated December 2020)**, p. 17, recommendation 1.3.17, p.35 (Rationale and Impact)

iii) NICE Guideline NG3; Methods, evidence and recommendations. December 2020.

E) i) A Type 1 diabetes technology pathway: consensus statement for the use of technology in Type 1 diabetes. Choudhary P, Campbell F, Joule N, et al. Diabetic Medicine, **2019**, 36(5): 531-8, (page 534, Figure 1). DOI: 10.1111/dme.13933.

ii) JDRF webpage on 'NHS access to CGM for pregnant women with type 1 diabetes due to begin in England', 14 November **2020** (accessed on 12 February 2021)

F) Modelling potential cost savings from use of real-time continuous glucose monitoring in pregnant women with Type 1 diabetes.

Murphy, H.R., Feig, D.S., Sanchez, J.J., de Portu, S., Sale, A. CONCEPTT Collaborative Group. Diabetic Medicine, **2019**, 36(12). DOI: 10.1111/dme.14046.

G) i) Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range. Battelino, T., *et al.* Diabetes Care, **2019,** 42(8):1593-1603. DOI: 10.2337/dci19-0028.

ii) Clinical Trials ISRCTN56898625 and NCT03774186.

H) i) Diabetes Technology Use Among Pregnant and Nonpregnant Women with T1D in the T1D Exchange; Polsky S, Wu M, Bode BW, DuBose SN, Goland RS, Maahs DM, Foster NC, Peters AL, Levy CJ, Shah VN, Beck RW. 2018 Aug;20(8):517-523. DOI: 10.1089/dia.2018.0033.

ii) Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes - 2020 American Diabetes Association. Diabetes Care, **2020,** 43 (Supplement 1): S183-S192. DOI: 10.2337/dc20-S014. S186, 14.9, 14.10

I) Media release authorised by Greg Hunt MP, Liberal Party of Australia, Somerville,Victoria, 'Free access to glucose monitoring now available for thousands of people with type 1 diabetes' from danii.org.au, accessed on 18 March 2021.

J) Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies.

Kristensen K, *et al*. Diabetologia. 2019 Jul;62(7):1143-1153. DOI: 10.1007/s00125-019-4850-0.