Diabetes “Polypill”

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I have the following Conflicts of Interest to report:

- Stock Shareholder – None
- Speakers Bureau – NovoNordisk, Eli Lilly, Sanofi, Abbott, Medtronic
- Grants/Research – Johnson & Johnson, Medtronic, Abbott Diabetes Care
  - Consultant – Medtronic
  - Employee – None
  - No Other

I will not be speaking on off-label topics.
Diabetes Polypills?

• Data from trials & “real-world”
  – National Pregnancy in Diabetes (NPID)/T1DEx

• Technology
  – Insulin Pump therapy (CSII)
  – Continuous Glucose Monitoring (CGM)
  – Automated closed-loop insulin delivery

• Diabetes education
  – Diet and Exercise
National Pregnancy in Diabetes (NPID) 2016

Mandatory National Audit N=172 antenatal services

- 3,297 women (1618 T1D, 1608 T2D)
- 3,356 births (1534 T1D, 1541 T2D)

http://digital.nhs.uk/catalogue/PUB30109
Diabetes Pregnancy outcomes

<table>
<thead>
<tr>
<th></th>
<th>All diabetes</th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
<th>Other(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>3297</td>
<td>1618</td>
<td>1608</td>
<td>71</td>
</tr>
<tr>
<td>Pregnancies (^b)</td>
<td>3304</td>
<td>1623</td>
<td>1610</td>
<td>71</td>
</tr>
<tr>
<td>Total pregnancy outcomes (^c)</td>
<td>3356</td>
<td>1650</td>
<td>1633</td>
<td>73</td>
</tr>
<tr>
<td>Pregnancies ongoing after 24 weeks</td>
<td>3091</td>
<td>1506</td>
<td>1517</td>
<td>68</td>
</tr>
<tr>
<td>Live births after 24 weeks</td>
<td>3108</td>
<td>1517</td>
<td>1521</td>
<td>70</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>32</td>
<td>16</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Total infants born after 24 weeks</td>
<td>3140</td>
<td>1533</td>
<td>1537</td>
<td>70</td>
</tr>
<tr>
<td>Live births with gestation unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Live births before 24 weeks</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Neonatal deaths</td>
<td>31</td>
<td>10</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Total registered births</td>
<td>3145</td>
<td>1534</td>
<td>1541</td>
<td>70</td>
</tr>
</tbody>
</table>

2.5 fold reduction in stillbirths since CEMACH (10.7 vs 25.8/1000 T1D \(^p = 0.0012\); 10.5 vs 29.2/1000 T2D, \(^p = 0.0091\))

Murphy HR et al, Diabetologia 2017 Sep;60(9):1668-1677, [http://digital.nhs.uk/catalogue/PUB30109](http://digital.nhs.uk/catalogue/PUB30109)
Who achieved target HbA$_{1c}$ in first trimester?

- Older, shorter diabetes duration, less deprived, CSII

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yrs)</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Median diabetes duration (yrs)</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Median BMI (kg/m$^2$)</td>
<td>25.5</td>
<td>26.2</td>
</tr>
</tbody>
</table>

21% used CSII (n=344). 20% on CSII vs 13% on MDI had target HbA1c
Clinic-to-clinic variation in First Trimester HbA$_{1c}$

- T1D median was 14% (range 0-44%)

Percentage of pregnancies with first trimester HbA$_{1c}$ <48 mmol/mol, by clinic$^a$

$^a$ Includes services with at least 10 valid first trimester HbA$_{1c}$ records: Type 1 diabetes – 107 services
Clinic-to-clinic variation in Third Trimester HbA$_{1c}$

- T1D median was 38% (range 0-82%)

Percentage of pregnancies with third trimester HbA$_{1c}$ <48 mmol/mol, by clinic$^a$

$^a$ Includes clinics with at least 10 valid 3rd trimester HbA$_{1c}$ records: Type 1 diabetes – 126 services

Direction of better performance
Obstetric and perinatal morbidity

- LGA 47% in T1D, 23% in T2D offspring
- 43% T1D and 21% T2D preterm < 37 weeks
- 60% T1D preterm and 50% T2D preterm NICU

Murphy HR et al, Diabetologia 2017 Sep;60(9):1668-1677, http://digital.nhs.uk/catalogue/PUB30109
CSII rationale

[Diagram of insulin injection and pump therapy]

Pickup J NEJM 2012
## Pumps during pregnancy

- **Benefit** of pump use. **Cohort studies**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Baseline</th>
<th>Glycemic control</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonzalez-Romero 2010</td>
<td>≠</td>
<td>1st T lower HbA1c 3rd T higher HbA1c</td>
<td>≈</td>
</tr>
<tr>
<td>Cyganek 2010</td>
<td>≠</td>
<td>more SH</td>
<td>higher WG more CS</td>
</tr>
<tr>
<td>Chico 2010</td>
<td>≠</td>
<td>≈</td>
<td>≠ after adjust.</td>
</tr>
<tr>
<td>Brutomesso 2011</td>
<td>≠</td>
<td>lower HbA1c</td>
<td>≈</td>
</tr>
<tr>
<td>Kallas-Koeman 2014</td>
<td>≠</td>
<td>lower HbA1c</td>
<td>more LGA</td>
</tr>
<tr>
<td>Mello 2015</td>
<td>≈</td>
<td>1st T lower pp glu</td>
<td>≈</td>
</tr>
<tr>
<td>Kekalainen 2016</td>
<td>≠</td>
<td>≈</td>
<td>≈</td>
</tr>
<tr>
<td>Abell 2017</td>
<td>≠</td>
<td>≈</td>
<td>≈</td>
</tr>
</tbody>
</table>
2007 CD 005542: “There was a significant increase in mean birth weight associated with CSII weighted mean difference 220.56, 95% CI -2.09 to 443.20”

2010 HTA: “This systematic review does not show any advantage or disadvantage of using CSII over MDI in pregnant diabetic women”

2012 Yeh AHRQ: “The Strength of evidence regarding pregnant women with diabetes was either low or non-existent on all outcomes”
In CONCEPTT cohort analysis

During CONCEPTT T1D pregnancy trial

MDI users

- larger HbA$_{1c}$ decrease
- $\approx$ time in target
- $\approx$ time above target
- $\uparrow$ time below (10-15mins)
- less decline in QoL

CSII users

- $\uparrow$ gestational HT
- $\uparrow$ preterm births
- $\uparrow$ NICU admissions
- $\approx$ Birthweight outcomes
- less hypo worry
Matching insulin to food in real-life?

"OK, constant monitoring, and watching, and counting has taken over. My life is not as free as it used to be in so far as you took 4 injections a day, and you just went about your business. But now every morsel of food over 10 grams of carbohydrate requires an injection" (P91-35 6 months)

becoming “a lot more conscious of my carb intake, and a lot of the time, like having a turkey breast or something, before I might have rice with it, whereas now I’m thinking, I’ll just have salad. I’m realising that, because I’m not having rice, I don’t need my insulin, and then I won’t have a hypo” (R2).

Casey et al, BMC Public Health 2011
CSII stable basal insulin replacement
Measuring Maternal/Fetal Glycaemia
Measuring Maternal/Fetal Glycaemia

Gestation (weeks)

Time with BGL 3.9-7.8 (%)

Type 1 DM
Type 2 DM

p=0.0001 T1 vs T2 DM
p<0.0001 increase over time

Murphy HR Diab Care 07
Continuous Glucose Monitor (CGM)

- **REAL-Time Trend Graphs**: Show the effect of diet, exercise, medication and lifestyle on glucose levels.
- **REAL-Time Alarms**: Protect patients by warning of low and high glucose levels.
- **REAL-Time Readings**: Help patients take action sooner.
  - Up to 288 glucose readings per day... every 5 minutes, 24 hours a day.
- **Wireless Transmitter**: Small, discreet, and waterproof.
- **Glucose Sensor**: Point up or down to show the direction and rate of change in glucose levels.
Primary Outcome: Change in HbA1c from randomisation to 34 weeks’ gestation

mean difference -0.2%
95% CI -0.34, -0.03
p = 0.0207
### % Time in target range 3.5-7.8mmol/L

<table>
<thead>
<tr>
<th></th>
<th>Pregnant</th>
<th>Baseline</th>
<th>Week 34</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CGM N=107</td>
<td>Control N=107</td>
<td>CGM N=77</td>
</tr>
<tr>
<td>% CGM 3.5-7.8 mmol/L</td>
<td>52% ± 13%</td>
<td>52% ± 14%</td>
<td>68% ± 13%</td>
</tr>
<tr>
<td></td>
<td>12.5hrs/day</td>
<td>12.5hrs/day</td>
<td>16.3hrs/day</td>
</tr>
</tbody>
</table>

**CGM mothers spent an extra 100 minutes/day in glucose target range**

Pump = Pens
N=31 sites

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Yamamoto J et al Current Diabetes Reports 2018
Impact of CGM on infant health outcomes

- **LGA**: 53% CGM vs 69% control
  - OR 0.51; 95% CI 0.28-0.90
  - p=0.0210
  - NNT 6

- **Hypoglycaemia** requiring dextrose infusion
  - 15% CGM vs 28% control
  - OR 0.45; 95% CI 0.22-0.89
  - p=0.0250
  - NNT 8

- **NICU admission >24h**: 27% CGM vs 43% control
  - OR 0.48; 95% CI 0.26-0.86
  - p=0.0157
  - NNT 6

Feig DS Lancet 2017
## Infant length of hospital stay

<table>
<thead>
<tr>
<th></th>
<th>CGM</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=100</td>
<td>N=100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of hospital admission days</td>
<td>455</td>
<td>697</td>
<td></td>
</tr>
<tr>
<td>Median (IQR) infant hospital stay</td>
<td>3.1 (2.1-5.7)</td>
<td>4.0 (2.4-7.0)</td>
<td>0.0157</td>
</tr>
</tbody>
</table>
"Dear Machines: You Can Take This Job"

<table>
<thead>
<tr>
<th>OPENAPS.ORG</th>
<th>What is OpenAPS?</th>
<th>Frequently Asked Questions</th>
<th>OpenAPS Reference Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>#WeAreNotWaiting to reduce the burden of type 1 diabetes</td>
<td>Outcomes</td>
<td>In The News</td>
<td></td>
</tr>
</tbody>
</table>

**OpenAPS Is Designed For Safety**

OpenAPS means basic overnight closed loop APS technology is more widely available to anyone with compatible medical devices who is willing to build their own system.

**How Do I Get Started?**

The documentation and reference design implementation code is available on Github. Take a look below for FAQs, reference design, and links to open source repository and documentation.

**Does It Really Work For Everyone?**

OpenAPS follows the same basic diabetes math that a person would do to calculate a needed adjustment to their BG – but it is automated and precise.

http://labs.teague.com/?p=2035
1. Continuous glucose monitor
2. Control algorithm device
3. Insulin pump
SAP vs closed loop glycaemic profiles

**SAP**

**Closed loop**
HOME Closed-Loop in Pregnancy
(CLIP_03, CLIP_04)

NEJM 2016, Diab Care 2018
In-patient closed-loop use

• 30 participants used day and night closed-loop for up to 14.4 weeks (14 CLIP_03 and 16 CLIP_04)

• Closed-loop was used across a range of pregnancy challenges including:
  – Admissions to obstetric wards
  – Antenatal steroid administration
  – Labour and delivery (vaginal, elective, and emergency c-section under spinal and GA)
  – Rapid reduction in insulin requirements post-delivery

NEJM 2016, Diab Care 2018
Labour & Delivery (n=27/32 women 85%)

- 4 NVD and 23 caesarean-section
  - 11 prior to onset of labour, 12 emergency
  - Spinal, epidural and general anaesthetic
  - 1 ovarian cystectomy
- No severe hypos or SAE or SADE

<table>
<thead>
<tr>
<th></th>
<th>24hrs prior to delivery</th>
<th>48hrs post-delivery*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% time in target range</td>
<td>82.0 (IQR 49.3, 93.0)</td>
<td>83.3 (75.2, 94.6)</td>
</tr>
<tr>
<td>% time &lt; below target</td>
<td>0.0 (0, 2.2)</td>
<td>2.5 (0.9, 5.8)</td>
</tr>
<tr>
<td>Number of hypoglycaemic events &gt;20mins</td>
<td>0</td>
<td>1.5 (1.0, 3.0)</td>
</tr>
<tr>
<td>Mean (SD) CGM glucose</td>
<td>6.9 (1.4)</td>
<td>7.2 (1.4)</td>
</tr>
</tbody>
</table>

*The antenatal target of 3.5-7.8 was adjusted to 3.9-10.0mmol/L immediately after delivery
There were no postnatal hypo events <3.5mmol/L

DTT 2018
Women’s views

“Its brilliant, it just took all the worry away, to be honest”

“I was using it even in my labour, my own closed-loop, because it was working fine in making me more relaxed”

“I’m going to miss all this technology to help control my sugars”

Concerns: “de-skilling”, “addiction”
Diabetes Pregnancy summary

• Use of insulin pump therapy has not improved maternal glucose control/pregnancy outcomes

• Use of CGM is associated with improved neonatal outcomes, attributed to reduced exposure to maternal hyperglycemia in T1D pregnancy (pumps and pens) – all centres

• Use of CGM in T1D pregnancy may be cost-effective (reduced NICU and 1-day shorter LOS)

• Potential for automated insulin delivery to reduce clinic-to-clinic variation

• Healthy diet and exercise are still essential in T1D
Measure glucose to treat diabetes!

“It’s like being completely blind and then having somebody open your eyes...
Managing my sugars without CGM is like driving a car blind folded....”
Practical take-Home Pearls

✩ Good data is essential for diabetes care
✩ Insulin pump therapy is not a polypill
✩ CGM best available “polypill”
✩ Automated insulin delivery may supersede
✩ Diet and exercise are still important
Questions