Type 1 DM Journey From Preconception to Breastfeeding

Marina Basina, MD
Stanford University
Endocrinology
Case report

On November 13th 1823 Frederica Pape was admitted to the Berlin Infirmary 7 months pregnant. She had “a really unquenchable thirst – consumed more than six Berlin measures of beer or spring water, the quantity of urine greatly exceeded the amount of liquids consumed”.

Treatment: 360 ml of venous blood withdrawal and high protein diet. On 12/29 she had an obstructed labor. The child died intrapartum. “The baby was such robust and healthy whom you would have thought Hercules had begotten”. Baby’s weight was 12 lbs.
Medical researcher **Frederick Banting** and research assistant Charles Best studied the islets of Langerhans in the pancreas of dogs at the University of Toronto. Banting believed that he could find a cure for the "sugar disease" (diabetes) in the pancreas. In 1921, they isolated insulin and successfully tested it on diabetic dogs, lowering the dogs' blood sugar level.

**1922**

**Frederick Banting Treats Leonard Thompson with insulin**
Reproduction and T1DM

- Increasing incidence of T1D worldwide, of 2-3% every year
- 40% of T1D female have menstrual disturbances, hyperandrogenism, or early menopause
- Combined effect of insulin deficiency and hyperglycemia
- Intensive insulin therapy with improvement of metabolic control improved reproductive function
- Insulin is an important regulator of HPG axis
- Poor metabolic control → hypogonadotrophic hypogonadism

- In uncontrolled DM – low basal LH, FSH, reduced pulsatility, disturbed negative feedback
**Insulin physiology**

- **Insulin** is secreted in response to fluctuations in BG levels – **hormone of “abundance”** → stores excessive nutrients:
  - as glycogen in the liver,
  - fat in adipose tissue,
  - and protein in the muscle
- Insulin is delivered peripherally at high concentrations with the goal of achieving normal concentration in the liver → systemic or peripheral hyperinsulinemia → increased food intake, weight gain
T1D and Ovarian Function

- Intensive therapy → decrease in amenorrhea from >20% to <10%, delay in menarche from several years to some months
- Reproductive abnormalities due to insulin excess:
  - hyperandrogenism
  - polycystic ovaries
  - excessive weight gain
- Insulin receptors present in most tissues
  - Subcutaneous insulin administration omits liver first pass metabolism and exposes peripheral tissues to supra-physiologic levels
Type 1 Diabetes Mellitus

- Insulin deficiency
  - Catabolic state†
    - ↓ leptin †
    - ↓ Kisspeptin*
      - ↓ GnRH secretion
        - ↑ Glucose levels
          - ↓ LH/FSH secretion
            - Hypogonadism
              - Pubertal delay
              - Menstrual irregularities
            - ↑ Androgen levels

- Subcutaneous insulin administration omits hepatic first pass clearance of insulin
  - Hyperinsulinemia
    - Ovarian insulin & IGF-I receptor
      - Theca cell
        - Adrenal Reticularis
        - Polycystic ovarian morphology
      - Granulosa cell
        - Follicular recruitment
      - Ovarian stroma
        - Exposure of the ovary to ↑insulin
          - ↑ insulin
          - EARLY MENOPAUSE

- Hyperglycemia
  - Glucose toxicity
    - AGE & RAGE in the ovary
      - Abnormalities in folliculogenesis
        - Apoptosis of follicles*
        - EARLY MENOPAUSE
Preconception Visit

- **Increased risks of:**
  - Preterm delivery
  - Pre-eclampsia
  - Perinatal mortality
  - Macrosomia
  - Congenital malformations

<table>
<thead>
<tr>
<th>Contraception use until recommended glycemic control is reached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deciding on the mode of intensive insulin therapy – pump, MDI, and insulin type</td>
</tr>
<tr>
<td>Intensification of treatment to achieve target control &lt;6.5%</td>
</tr>
<tr>
<td>Revision of concomitant therapy (antihypertensive, cholesterol)</td>
</tr>
<tr>
<td>Comprehensive re-education</td>
</tr>
<tr>
<td>Thyroid function assessment</td>
</tr>
<tr>
<td>Supplementation of Folic acid (at least 400 mcg per day)</td>
</tr>
<tr>
<td>Evaluation and treatment of chronic complications, urine MA, retinal exam</td>
</tr>
</tbody>
</table>
Psychological Issues with Transition to Motherhood

- Major life changing event
- **Specific stressors:** intensive glucose management, increased frequency of hypoglycemia, fear of losing control of the body and diabetes, anxiety about adverse pregnancy outcomes, meticulous planning of daily activities, frequent contacts with health care providers
- high levels of worrying, depression, guilt and fear of being a ‘burden’ to others
- Supportive role of partners and health care team is crucial in all phases of transition (pre-pregnancy, pregnancy, post-partum)
- The web-based support is very important provided it contained reliable information, improved access to health professionals, offers interactive support and social networking during pregnancy and after giving birth
Initial Visit Evaluation

- Review of the medical history, previous pregnancy/obstetric complications, DM complications
- Review of eating patterns, physical activity, psychosocial problems
- Setting expectations and formulating management plan
- Lab tests: A1C, TSH +/- Free or Total T4, creatinine/kidney function, urine microalbumin (if on a high side of normal, 24 hour urine for protein excretion), liver enzymes, hemoglobin, hematocrit, iron (if anemia)
- Blood pressure >140/90 should be treated
- ACEI and ARB are contraindicated
- Dilated eye exam in the 1st trimester of pregnancy
- No retinopathy – 1st and 3rd trimesters, mild – every trimester, moderate to severe - monthly
Blood Glucose Targets

- Fasting – less than 95 mg/dl
- 1 hour post-meal \( \leq 140 \) mg/dl
- 2 hour post-meal \( \leq 120 \) mg/dl
Maresh et al, Diab Care 2015 – 725 women with T1D assessed prospectively

- A1C 6-6.4% at 26 wks associated with increased risk for LGA
- A1C 6.5-6.9% - increase in preterm delivery, pre-eclampsia, need for neonatal glucose infusion, and composite adverse outcome
- Progressive increase in the risks with increasing A1C

### A1C Targets During Pregnancy

<table>
<thead>
<tr>
<th>Trimester</th>
<th>A1C value</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{st})</td>
<td>6-6.5%</td>
<td>If can be achieved w/o hypoglycemia</td>
</tr>
<tr>
<td>2(^{nd})</td>
<td>&lt; 6%</td>
<td>Can be relaxed to prevent hypoglycemia</td>
</tr>
<tr>
<td>3(^{rd})</td>
<td>&lt; 6%</td>
<td>Same</td>
</tr>
</tbody>
</table>

Composite – perinatal death, shoulder dystocia, fractures, nerve palsy, admission to NICU for level 2-3 care
Assessment of Metabolic Control

- Urine ketones at times of illness or BG >200
- A1C at the initial visit, monthly until at target, then every 2-3 months
- Regular access to health care team by phone or other in between-visits
- DKA develops faster during the pregnancy, associated with high fetal mortality
- Ketones in poorly controlled DM – decreased intelligence, fine motor skills
- SBGM before and after the meals, fingersticks are best (alternate sites are not good for rapid glucose changes)
- CGM as a supplemental tool
Nutrition in Pregnancy

- WHO guidelines – increased energy needs in the 2nd and 3rd trimester.
- T1D women – restrict gestational weight gain to lower limits of IOM guidelines (table) and strict glycemic control
- 45-65% carbohydrates, 10-35% protein, 20-35% fat
- **GI** – area under the blood glucose curve during the initial 2 hours after ingestion of 50 g of test food (glucose or white bread)

<table>
<thead>
<tr>
<th>Prepregnancy BMI</th>
<th>Total weight gain Range in kg</th>
<th>Rates of weight gain in 2nd and 3rd trimester Mean (range) in kg/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt;18.5 kg/m²)</td>
<td>12.5–18</td>
<td>0.51 (0.44–0.58)</td>
</tr>
<tr>
<td>Normal weight (18.5–24.9 kg/m²)</td>
<td>11.5–16</td>
<td>0.42 (0.35–0.50)</td>
</tr>
<tr>
<td>Overweight (25.0–29.9 kg/m²)</td>
<td>7–11.5</td>
<td>0.28 (0.23–0.33)</td>
</tr>
<tr>
<td>Obese (≥30.0 kg/m²)</td>
<td>5–9</td>
<td>0.22 (0.17–0.27)</td>
</tr>
</tbody>
</table>
Nutrition in Pregnancy

• Glycemic load = amount of carb x GI
• Low GI diets – positive effects in GDM, healthy pregnancy, reduction of gestational weight gain, non-pregnant T1 and T2D.
• Carb count with all meals and snacks – generally recommended, no data in pregnancy
• Low carb diets – reduce the risk of hyperglycemia
• Jovanovic et al. moderately low (40%) or low (35%) – reduced need for insulin and macrosomia in GDM
• Concern of induction of ketogenesis due to accelerated maternal fasting ketogenesis
• Ideal amount of carbs is unknown
Recommendations

• Moderately low carb diet with 40% of the calories as carbs and intake of at least 175 grams of carb daily
Carb Distribution Throughout the Day

- 20 grams breakfast (10-15%)
- 40 grams lunch and dinner (30%)
- 2-4 snacks 10-20 grams each
- Timing of meals and snacks to prevent both hyper- and hypoglycemia
Insulin Therapy

• All insulins are pregnancy category B except for Glargine (Lantus), glulisine (Apidra), and Degludec
• 1st trimester – 7-12 weeks (up to 14 weeks) decline in insulin requirements
• Possible explanations:
  • - over-insulinization of previously poorly controlled diabetes
  • - transient decline in progesterone secretion during the late first-trimester luteo-placental shift in progesterone secretion (from corpus luteum to placenta) – nadir of progesterone at week 8, remains below the peak till 16 weeks
• Average dose reduction of 34% (Jovanovic et al)
• Warning for hypoglycemia
2\textsuperscript{nd} and 3\textsuperscript{rd} Trimesters Insulin Requirements

- Pregnancy is a state of insulin resistance due to Placental Lactogen
- \textit{Basal insulin} increase from week 16 and onwards
- Adjust based on fasting and pre-prandial glucose values

- Meal bolus – adjust based on post-meal values
- 4-fold decline in CHO is common
- Bolus given 15-30 min before meals especially in late gestation
Insulin Requirements (cont.)

- **Insulin sensitivity factor**: reduction after 16 weeks following adjustment in ins-to-carb ratio
- Insulin requirement usually levels out about 36 weeks on
- 10-20% usually fairly abrupt drop 36-37 weeks – exercising uterus, check 2-3 AM blood sugar and reduce insulin accordingly. May be a sign of placental insufficiency
- **Labor** – intravenous insulin infusion, blood glucose target is under 110 mg/dl to prevent fetal hyperglycemia and subsequent neonatal hypoglycemia and long term neurological sequelae
- Insulin requirements decrease during induction in up to 50% of women
Insulin During Labor

- Active labor – further decrease, increase need for glucose
- Expulsion of fetus-placenta → reduction of insulin resistance mediating hormones → improvement of sensitivity → increased risk of hypoglycemia – 75% glucose only infusion and discontinuation of insulin infusion
- In elective c-section – 25-50% basal insulin dose reduction starting the evening before delivery
Apparent Transient Insulin Independence

- May last 24-72 hours
- 80% of women require less than pre-pregnancy insulin dose for 2 days after delivery
- Considerable glucose variability postpartum with trend to increased hypoglycemic episodes
- Suggested that insulin be recommenced at 25-50% of pregnancy dose or 2/3 of pre-pregnancy dose
Breastfeeding and Insulin Requirements

- Metabolic effect of gestation – 50 g of glucose daily diverted to lactogenesis (process of milk synthesis and secretion) via non-insulin mediated pathway
- Jovanovic, 2009 – basal insulin dose of 0.21 u/kg/day
**Risk and Significance of Hypoglycemia**

*Diab Medicine 2012*

- **Definition of severe hypoglycemia (HG):** event with symptoms of hypoglycemia requiring help from another person to administer oral carbohydrates or inject glucagon or glucose to restore the blood glucose level.
- It is the main obstacle and limit for achievement of strict control.
- Severe HG is 3-5 times more frequent in early pregnancy comparing to before the pregnancy but lower incidence in 3rd trimester.
- Up to 45% of women experience severe HG during the pregnancy with 80% of the events occurring before week 20 of gestation.
• Pre-bedtime glucose of less than 98 mg/dl predicts nocturnal hypoglycemia
• Pregnancy itself can impair counter-regulatory hormonal response to HG (threshold is lower 48-57 mg/dl during gestation)
• Attenuated sympathetic neural activation \(\rightarrow\) HG unawareness
• **Normal hormonal response to HG:** release of adrenaline, glucagon, cortisol, and Growth hormone.
• In type 1 pregnancy – failure to elicit increased glucagon, lower blood glucose threshold for adrenaline release especially in 3\(^{rd}\) trimester comparing to non-pregnant woman.
• Larger dependency on cortisol and growth hormone response.
• Placental growth hormone increases during 3\(^{rd}\) trimester
• No residual beta-cell function (C-peptide negative) increases the risk of severe HG.
HG (cont.)

• Pregnancy induces increase in C-peptide in late pregnancy in C-peptide positive women and sometimes detectable levels C-p in negative (protection against HG in late pregnancy)

• Risk factors for severe hypoglycemia during pregnancy

<table>
<thead>
<tr>
<th>History of severe hypoglycemia the year preceding pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-estimated impaired hypoglycemia awareness</td>
</tr>
<tr>
<td>A longer duration of diabetes</td>
</tr>
<tr>
<td>A lower HbA1C in early pregnancy</td>
</tr>
<tr>
<td>Fluctuating plasma glucose values</td>
</tr>
<tr>
<td>Excessive supplementary insulin between meals</td>
</tr>
</tbody>
</table>
Hypoglycemia Prevention

• Early identification of patterns
• Proactive insulin dose reduction by 10-20% at 8-16 weeks
• Precautious use of supplementary insulin in early pregnancy
• Carry glucose – cup of milk 14 gr (8 oz) or 3-5 glucose tabs 12-20 gr; OJ 22 gr for BG <50
• Avoid bedtime glucose values under 110
• Frequent glucose monitoring
• Glucagon emergency kit
• Use of CGM
Physical Activity and Glucose Control in Pregnancy T1D (Diab Care, 2013)

- 1st study to evaluate impact of structured physical activity on glucose control
- **Controlled study conditions:** FreeStyle Navigator CGM, not visible to women, venous blood samples every 15-30 min. Animas pump used
- **Activity schedule:**
  - 3 x 20 min self-paced post-prandial walks (after breakfast, lunch, dinner),
  - afternoon treadmill – 25 min walking 3 miles/h, 5 min rest, 25 min 1.6 miles/hr at 10% incline,
  - Morning - 2 x 25 min walking 3 miles/h, 5 min rest in between
Exercise

- Free living – usual daily routine
- CGM mmol/L
- Physical activity energy expenditure (kcal/kg) (PAEE)
- **Free living** – 10.3 hrs (43%) time spent in light intensity activity, 27 min (2%) in moderate intensity, highest PAEE between 7 and 9 am
- **Controlled study** – 7.2 hrs (30%) and 121 min (8%)
### Exercise in T1D Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Free Living</th>
<th>Controlled Study</th>
<th>P value &lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time spent above the target</td>
<td>28%</td>
<td>17%</td>
<td>0.059</td>
</tr>
<tr>
<td>Mean CGM glucose</td>
<td>139 mg/dl</td>
<td>108 mg/dl</td>
<td>0.028</td>
</tr>
<tr>
<td>Morning glucose</td>
<td>Closer to target</td>
<td>Higher after 50 gr carb breakfast</td>
<td>NA</td>
</tr>
<tr>
<td>Hypoglycemia overall (%)</td>
<td>2%/2</td>
<td>5%/1.7 – 1.7/subject/day</td>
<td>0.161</td>
</tr>
<tr>
<td>Overnight mean CGM/time in hyperglycemia</td>
<td>135 mg/dl 19%</td>
<td>94 mg/dl 0%</td>
<td>0.047 0.028</td>
</tr>
</tbody>
</table>

- **Hypoglycemia** – 65% of HG in controlled group occurred during or within 2 hrs of moderate intensity treadmill. Only one episode after MN in subject who had 4 earlier episodes in the afternoon
- Nocturnal SD (variability) – decreased by 50% in controlled study group
Exercise in TID Pregnancy

• **Conclusions:**
• More attention to daily dietary and physical activity
• Encourage to walk for 20 minutes after each meal is a practical way of increasing physical activity (current recommendation is 30 min of moderate intensity activity per day)
• Hypoglycemia remains a limitation to exercise
• Structured diet and exercise can improve glycemic control
Summary

- A healthy pregnancy for women with type 1 diabetes starts before conception.
- Type 1 diabetes can be a challenge in pregnancy, but with education, close monitoring, and latest therapeutic modalities, these women can have healthy newborns.
- Close attention to diet, glycemic control, metabolic stresses, and early diagnosis and monitoring of complications can make pregnancy a successful and not stressful experience.
- Diabetes should not stop you from experiencing the possibility of having children.
- Educate yourself as much as possible, make a commitment to yourself, and put your baby first as much as you can while you are pregnant.
Thank you