Simposio 9
Diabete Gestazionale
Moderatori: F. Calcaterra, G. Lovenio
Criteri Diagnostici: M. Nizzoli
Obiettivi Terapeutici: R. Volpe
Terapia durante la Gestazione: M. Bonomo
Parto e Puerperio: Angela Napoli
Take Home Messages: E. Di Naro
PARTUM

Vaginal

Cesarean Section

Spontaneous
Induced

General Anesthesia
Epidural/Spinal Anesthesia

Post-Partum

with Breast feeding
without Breastfeeding
Great Energy Consumption

a) Il Travaglio Attivo di Parto è una forma di
Esercizio Fisico
Aumentata Richiesta Energetica (≥40%)

b) Alto Turnover di Glucosio ⇒ x 8 il Fabbisogno di
Glucosio

Fabbisogno di Glucosio Costante

2,5 mg/Kg/min

150 mg/Kg/h
Correction Factors to be applied on the Estimated Energy Expenditure according to Pathology and Physical Activity

*(Long, Wilmore, Clifton)*

<table>
<thead>
<tr>
<th>Pathology</th>
<th>%BMR</th>
<th>Stress Factor (SF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective Surgery</td>
<td>0-10</td>
<td>1.0-1.10</td>
</tr>
</tbody>
</table>

*Ambulatory Patients ‘Physical Activity Factor’ (PAF) = 1.25-1.5*

*Total Energy Expenditure = %*(BMR)* x (PAF) x SF*
Glycemic Targets during Delivery of Diabetic Pregnant Women

<table>
<thead>
<tr>
<th></th>
<th>Jovanovic</th>
<th>Ryan</th>
<th>Lepercq</th>
<th>De Valk</th>
<th>Klein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Glucose</td>
<td>70 - 90 mg/dl</td>
<td>70 - 120 mg/dl</td>
<td>70 - 140 mg/dl</td>
<td>72 - 144 mg/dl</td>
<td>72 - 117 mg/dl</td>
</tr>
<tr>
<td>mMol/L</td>
<td>3.9 - 5.0</td>
<td>3.9 - 6.6</td>
<td>3.9 - 7.7</td>
<td>4.0 - 8</td>
<td>4.0 - 6.5</td>
</tr>
</tbody>
</table>

...per prevenire l’ipoglicemia neonatale, i valori glicemici devono essere mantenuti entro valori molto ristretti (tra 70 e 120 mg/dl secondo alcuni autori, tra 70 e 90 mg/dl secondo l’ADA).
A Delicate Balance should be struck between preventing Hyperglycaemia and Hypoglycaemia

- BG > 150mg/dl → ↑ Risk of Fetal Hypoxia
- BG > 90 or >110mg/dl → ↑ Fetal Hypoglycemia
- BG <100mg/dl → ↓ Fetal Hypoglycemia
- Maternal Hypoglicemia → ↑ Fetal Hypoglycemia

Maternal Chetonemia è potentially dangerous for Fetus
Protocol of Insulin Therapy during Vaginal Delivery or CS Double I.V. Infusion Route

Glucose 10%

80ml/h

Check CBG at baseline then hourly:

- <70mg/dl \( \Rightarrow \) stop insulin
- 70-140mg/dl \( \Rightarrow \) insulin: 1unit/h
- >140mg/dl \( \Rightarrow \) insulin 1.5-2 units/h
- ≥180-200mg/dl \( \Rightarrow \) insulin 3 units/h*

*If confirmed a second time, stop glucose until the following CBG

Regular Insulin 50 units + 50ml di NaCl 0.9

New Technologies, such as CSII &/or CGM have been rapidly increasing becoming more & more frequent during

Preconception Care & Subsequent type 1 Diabetic Pregnancies

- to Achieve Optimal Metabolic Control, Without Increased Risk of Maternal Hypoglycemia
- to Prevent Maternal Fetal Adverse Outcomes
CSII DURING DELIVERY IN WOMEN WITH DIABETES
Experiences of CSII in Pregnant Women with Type 1 Diabetes During Delivery from four Italian Centers: A Retrospective Observational Study

R. Fresa · N. Visalli, V. Di Blasi · V. Cavallaro · E. Ansaldi · O. Trifoglio · S. Abbruzzese, M. Bongiovanni, M. Agrusta, A. Napoli,
Multicenter Observational Retrospective Study

Primary Aim:
To evaluate the Efficacy and Safety of Continuous Subcutaneous Insulin Infusion (CSII) during Delivery in Pregnant Women with type1 Diabetes.

Secondary Aim:
To assess the impact of real-time continuous glucose monitoring (RT-CGM) added to CSII versus CSII alone.
END POINTS

EFFICACY
- Maternal CBG values at TARGET (70–140 mg/dL; 3.8–7.7 mMol/L) in 4 specific moments: at admission, 0 min [immediately before anesthesia or at the beginning of the second stage of labor], 30 min, and 60 min
- Frequency of Neonatal Hypoglycemia or Cumulative Respiratory Disorders

SAFETY
- Frequency of Maternal hypoglycemia (CBG ≤50 mg/dL [2.7 mmol/L]) throughout delivery
- Number of Women switching to the i.v. protocol (IVP)
<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Total Sample</th>
<th>CSII</th>
<th>RT-CGM</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>65</td>
<td>47</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>31±5</td>
<td>30.5±5</td>
<td>32±6</td>
<td>NS</td>
</tr>
<tr>
<td>Duration (yrs)</td>
<td>16±8</td>
<td>15±8</td>
<td>17±10</td>
<td>NS</td>
</tr>
<tr>
<td>Preg. BMI kg/m²</td>
<td>24±3</td>
<td>25±4</td>
<td>24±2</td>
<td>NS</td>
</tr>
<tr>
<td>Multiparity</td>
<td>31 (48%)</td>
<td>26 (55%)</td>
<td>5 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pregestational HbA1c (%)</td>
<td>6.6±1</td>
<td>6.7±1.4</td>
<td>6.3±1</td>
<td>NS</td>
</tr>
<tr>
<td>3rd trimester HbA1c (%)</td>
<td>5.9±2b</td>
<td>6.2±1.7</td>
<td>5.2±0.4c</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Planned Preg(n)</td>
<td>25 (38%)</td>
<td>15 (32%)</td>
<td>10 (55%)</td>
<td>NS</td>
</tr>
<tr>
<td>Schooling (yrs)</td>
<td>13±3</td>
<td>13±3</td>
<td>13±2</td>
<td>NS</td>
</tr>
</tbody>
</table>

39 Women started CSII during pregnancy
HbA1C was 7.1±1.3% at ‘entry’ & 6.6±1.5% at the 3rd trimester (NS)
No difference in the 3rd trimester HbA1c between this subgroup and either group
Education Program

Initially, our only resource:
- Our PATIENT and her pump
- Education program from the FIRST VISIT
- Education program from the 28° WEEK

Later, more resources:
- PARTNER/CARE GIVER, DELIVERY ROOM TEAM
- insulin pump use or sensor augmented sytem during delivery
- Intravenous Insulin Protocol*

*J. Lepercq, A standardized protocol to achieve normoglycaemia during labour and delivery in women with type 1 diabetes Diabetes & Metabolism 34 33–37, 2008
Research Design and Methods

Standardized protocol with CSII throughout Pregnancy & Delivery
3 different insulin Basal Rates/Profiles according to C.B.G. Levels

<table>
<thead>
<tr>
<th>PROFILE A</th>
<th>PROFILE B</th>
<th>PROFILE C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Rate in Use</td>
<td>50% Actual Basal Rate</td>
<td>0,1-0,2 U/h (CBG &lt; 70mg/dl)</td>
</tr>
</tbody>
</table>

An **Alternative** Intravenous Protocol (IVP) was given in case of complications and relevant metabolic deterioration

**Targets:** BG = 70–140 mg/dL throughout Delivery
THE PROTOCOL STARTS

- at the time of Admission in the case of CS or Spontaneous Labor
- 2 h after the Intravaginal Administration of Prostaglandin in Induced labor (IL)

Glucose infusion was started in case of a prolonged first phase of labor (>5 h), long lasting fasting state or persistent CBG value <70 mg/dL

Starting with Isotonic Saline Solution

Minimal Changes in Maternal Metabolic Demand & Prolongued Use of Glucose during Euglycemia (70-120mg/dl=3.9-6.6mmol/l) responsible for ↑ Incidence of Neonatal Hypoglycemia.

Correction Bolus based on Individual Insulin Sensitivity
CBG was monitored every 30 min until delivery

**Intravenous Glucose infusion:**
- 5% in case of CS
- 10% in case of Vaginal Delivery
  adjusted for CBG levels
<table>
<thead>
<tr>
<th>PROFILE A</th>
<th>PROFILE B</th>
<th>PROFILE C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Rate in Use</td>
<td>50% of Actual Basal Rate</td>
<td>0.1-0.2 U/h (CBG &lt; 70mg/dl)</td>
</tr>
</tbody>
</table>

1° Phase  
NaCl  
PROFILE A  
CBG every hour

CBG  
70-140mg/dl  
3.8-7.7mMol/L

2° Phase  
Glucose  
PROFILE B  
CBG every 30’
Table 3.  
C.B.G. values & I.B.R. in Different Modalities & Stages of Delivery
No Differences in Different Delivery Modalities

<table>
<thead>
<tr>
<th></th>
<th>Cesarean Section</th>
<th>Spontaneous Labor</th>
<th>Induced Labor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>56</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td><strong>At Admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBR (U/h)</td>
<td>1.4 ± 0.4</td>
<td>1.3 ± 0.4</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>CBG (mg/dL)</td>
<td>96 ± 24</td>
<td>98 ± 12</td>
<td>92 ± 18</td>
</tr>
<tr>
<td><strong>Anesthesia or Second Stage of Labor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBR (U/h)</td>
<td>1.4 ± 0.4</td>
<td>1.3 ± 0.4</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>CBG (mg/dL)</td>
<td>106 ± 33</td>
<td>77 ± 8</td>
<td>89 ± 19</td>
</tr>
<tr>
<td>30 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBR (U/h)</td>
<td>0.6 ± 0.4</td>
<td>0.6 ± 0.3</td>
<td>0.55 ± 0.1</td>
</tr>
<tr>
<td>CBG (mg/dL)</td>
<td>109 ± 42</td>
<td>94 ± 17</td>
<td>88 ± 4</td>
</tr>
<tr>
<td>60 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBR (U/h)</td>
<td>0.6 ± 0.4</td>
<td>0.4 ± 0.3</td>
<td>0.15 ± 0.1</td>
</tr>
<tr>
<td>CBG (mg/dL)</td>
<td>123 ± 49</td>
<td>101 ± 33</td>
<td>86 ± 9</td>
</tr>
</tbody>
</table>
Maternal & Fetal Outcomes:
Impact RT-CGM+CSII vs CSII during Delivery

Basal Rate during Delivery was $0.6 \pm 0.4$ U/h (PROFILE B)

CBG level was LOWER in the RT-CGM group vs CSII-alone group:

<table>
<thead>
<tr>
<th>Time</th>
<th>RT-CGM</th>
<th>CSII-alone group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>$80 \pm 14$ mg/dL</td>
<td>$111 \pm 32$ mg/dL</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>30 min</td>
<td>$79 \pm 11$ mg/dL</td>
<td>$109 \pm 42$ mg/dL</td>
<td>$&lt;0.02$</td>
</tr>
<tr>
<td>60 min</td>
<td>$98 \pm 20$ mg/dL</td>
<td>$125 \pm 51$ mg/dL</td>
<td>$ns$</td>
</tr>
</tbody>
</table>

None of the Women switched to IVP
**C.B.G. Values & I.B.R. in Peri-Partum Period**

<table>
<thead>
<tr>
<th></th>
<th>Prepartum</th>
<th>Delivery</th>
<th>24hr after</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTCG+CSII</td>
<td>90</td>
<td>85</td>
<td>122 mg/dl</td>
</tr>
<tr>
<td>CSII</td>
<td>114</td>
<td>127</td>
<td>122 mg/dl</td>
</tr>
</tbody>
</table>

**C.B.Glucose (mg/dl)**

**Average Insulin Infusion Rate (U/h):**
- **At ADMISSION PROFILE A:** 1.3 U/h T0'
- **DELIVERY PROFILE B:** 0.6 U/h T60'
- **ORAL FEEDING PROFILE B:** 0.5 U/h 24h
- **DELIVERY PROFILE C:** in 2/5 sl & 4/4il

86% of women
Conclusions

Safety of CSII

CSII can be Effective & Safe during Delivery in well-educated & Motivated Patients already under CSII during Pregnancy

LIMITS

Retrospective
Self Selected Population
No Control Group
Low Number of Vaginal Deliveries
Use of real time continuous glucose monitoring and intravenous insulin in type 1 diabetic mothers to prevent respiratory distress and hypoglycaemia in infants
Dario Iafusco*1, Fabrizio Stoppoloni†2, Gennaro Salvia†3, Gilberto Vernetti†2, Patrizia Passaro†1, Goran Petrovski†4 and

CGMS in 18 Type 1 diabetic Pregnant Women
a) during treatment with Betamethasone
b) during Delivery.
Insulin administered i.v. & the dose was changed on the basis of glycaemia

No Infant Experimented Hypoglycaemia or RDS at the Moment & in the First Hours after Birth

We wish to stress the importance reducing glycaemia during administration of betamethasone and during labor.
..Scarce attention paid to monitoring glucose levels in diabetic mothers during Labor may be due to the Difficulty in Glucose Monitoring with the Devices until now Available
Nel post-partum si ha una rapida e brusca diminuzione del fabbisogno insulinico; la terapia insulinica non dovrà essere ripristinata prima di un'ora dal parto e solo quando i valori glicemici siano costantemente superiori a 140 mg/dl
Puerperium

Period of Intense Hormonal & Metabolic Changes

Placental hormone blood levels, dramatically elevated during pregnancy, drop to virtually nil.

Insulin resistance, increased two-to three fold during pregnancy, returns to normal.

Lipoprotein levels elevated during pregnancy return to pre-pregnancy levels.
Lactation is Important Variable in this Period of Dynamic Metabolic Changes

Lactating vs Non Lactating

- **PRL**: 8 weeks postpartum with no difference between Type 1 Diabetes & Controls
- Estradiol: ↓
- Progesterone: ↓
- IRI: ↓
- AUC IRI after IVGTT: ↓
- Insulin sensitivity: ↑
- Insulin secretion: ↑
- Glucose: ↓
- Glucose intolerance: ↓

Estimated Energy Requirement of Lactating Women

Lactation is associated with an increase rates of Energy Intake & Expenditure for the:

- Cost of Milk & Lactose Synthesis
- Higher Rate of CHO utilization consistent with the preferential non-insulin mediated use of glucose by the mammary gland (50-60g/day)

possibly allowing a quicker return to pre-pregnancy weight as the extra body fat stored in pregnancy is now used for milk production
Lactation often associated with Beneficial Effects on CHO & Lipid Metabolism

**Fasting Insulin & LDL-C levels** decreased less at 3 years in women who had lactated at least 3 months compared with parous women who never lactated


**Middle aged Women** who breast-fed were less likely to have the **Metabolic Syndrome**: adjusted OR: 0.77

↓ Rate of **M.S.** with ↑ Duration of Breast-feeding

↓ Lower risks of Elevated **BP, Abdominal Obesity & IFG**.


Women without prior GDM reporting increased duration of breastfeeding were at **reduced risk of type2 diabetes** in the large Nurses’ health study

_Stuebe, JAMA 2005_
Metabolic Changes in ‘Diabetic’ Women
Does Lactation similarly affect women with recent GDM?

The Effect of Lactation (4-12 weeks) on Glucose & Lipid Metabolism in Women with Recent GDM

<table>
<thead>
<tr>
<th></th>
<th>Lactating (n=404)</th>
<th>Not-Lactating (n=405)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC-G (g.min/dl)</td>
<td>17.0±4.2</td>
<td>17.9±5.0</td>
<td>.01</td>
</tr>
<tr>
<td>Fasting Glucose (mg/dl)</td>
<td>93±13</td>
<td>98±17</td>
<td>.0001</td>
</tr>
<tr>
<td>2-hr Glucose (mg/dl)</td>
<td>124±41</td>
<td>134±49</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>17 (4.2%)</td>
<td>38 (9.4%)</td>
<td>.01</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>219±42</td>
<td>213±42</td>
<td>ns</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>48±11</td>
<td>44±10</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>136±35</td>
<td>131±35</td>
<td>ns</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>182±175</td>
<td>198±125</td>
<td>ns</td>
</tr>
</tbody>
</table>

S. Kjos, et al
Obstetrics and Gynecology, 1993
Breast-feeding in Pregestational Diabetic Women

Success of Breastfeeding is not associated with
- Diabetes-related parameters: diabetes duration or metabolic control.
- Route of delivery
- Parity
- Neonatal weight

Concerns
Frequent hypos in type 1 diabetic women

Riviello et al.
Breastfeeding and Insulin, Endocr Pract. 2009
Continuous Glucose Monitoring in Healthy Women
Mean Blood Glucose Levels of the 16th, 22nd, 30th weeks of gestation showed a tendency to increase, significantly higher in the 36th week.

At 6 weeks postpartum BG levels the same as during the 4th phase of the study. The results of the measurements with the portable glucose meters were similar.
Healthy women who had pregnancies uncomplicated by pregestational or gestational diabetes neither they did manifest significant changes in profiles/mean glucose levels during the period before or after lactation nor hypoglycemia in response to lactation.

Main study limitation: Sample size.

R. Bentley-Lewis et al. Diabetes Care 2009
Continuous Glucose Monitoring in prior-GDM
CGM during Breast-Feeding in Normotolerant Women (OGTT) With & Without Previous GDM

Prior-GDM/normotolerant at follow-up
Normotolerant in & out of pregnancy

Continuous Glucose Monitoring During Breastfeeding in Women with Recent Gestational Diabetes Mellitus
**CGM during Breast-Feeding: Comparison between studies**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>T. Siegmud 2008</th>
<th>Colatrella, Napoli Breast-feeding</th>
<th>Colatrella, Napoli Breast-feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.a. n=28</td>
<td>N/N □</td>
<td>PriorGDM/N ▲</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>29.6 ± 4.5</td>
<td>36.2 ± 3.4</td>
<td>35.2 ± 4.0</td>
</tr>
</tbody>
</table>

**Three months after Delivery:**
Non Diabetic Women with a history of GDM show worse daily glycemic profiles

| 72h CGM (mg/dL)     | 93.7 ± 9.0      | 87.5 ± 8.7                        | *101.4 ± 14.2                     |
| Daytime             | n.a.            | 89.0 ± 9.2                        | *99.4 ± 10.5                      |
| Night-time          | n.a.            | 84.8 ± 9.5                        | *N/N vs pG99/0 ± 10.5 Significant |
CGM during suckling: Comparison between studies

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Bentley</th>
<th>Colatrella, Napoli</th>
<th>Colatrella, Napoli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=9</td>
<td>N/N □</td>
<td>PriorGDM/N ▲</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>33 ± 4</td>
<td>36.2 ± 3.4</td>
<td>35.2 ± 4.0</td>
</tr>
<tr>
<td>Weeks after delivery</td>
<td>20.3 ± 7.3</td>
<td>13.1 ± 5.1</td>
<td>11.5 ± 3.7</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>24.4 ± 5.3</td>
<td>23.0 ± 1.6</td>
<td>* 25.9 ± 4.5</td>
</tr>
<tr>
<td>60’ pre-suckling glucose levels (mg/dL)</td>
<td>95.0 ± 14</td>
<td>80.4 ± 15.6</td>
<td>93.9 ± 15.7</td>
</tr>
<tr>
<td>60’ post-suckling glucose levels (mg/dL)</td>
<td>96 ± 15</td>
<td>80.3 ± 13.5</td>
<td>93.2 ± 14.5</td>
</tr>
</tbody>
</table>

Figure 1 — Blood glucose levels (mg/dL) collected every 5 min during the 60 min before and after the start of lactation (time = 0) for each of the nine participants in the study.
Tante Grazie

Angela Napoli