Simposio 9
Diabete Gestazionale
Moderatori: F. Calcaterra, G. Lovero

Criteri Diagnostici: *M. Nanzoli*
Obiettivi Terapeutici: *R. Volpe*
Terapia durante la Gestazione: M. *Bonomo*

Parto e Puerperio: *Angela Napoli*

Take Home Messages: *E. Di Naro*

12° Congresso Nazionale AME
Associazione Medici Endocrinologi
6th Joint Meeting with AACE
American Association of Clinical Endocrinologists

PARTUM

Vaginal	Spontaneous Induced
Cesarean Section	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

C.S. Energy Consumption

Correction Factors to be applied on the Estimated Energy Expenditure according to Pathology and Physical Activity

(Long, Wilmore, Clifton)

Pathology	%BMR	Stress Factor (SF)
Elective Surgery	*0-10*	*1,0-1,10*

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

...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**).

Jovanovic	70 e 90 *mg/dl*	3.9 - 5.0 *mMol/L*
Ryan	70 e 120	3.9 - 6.6
Lepercq	70-140	3.9-7.7
De Valk	72-144	4-8
Klein	72-117	4.0 - 6.5

METABOLIC CONTROL DURING DELIVERY

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

Regular Insulin 50 units + 50ml di NaCl 0,9

Check CBG at baseline then hourly:

- <70mg/dl ⇒ stop insulin
- 70-140mg/dl ⇒ insulin: 1unit/h)
- >140mg/dl ⇒ insulin 1,5-2 units/h
- ≥180-200mg/dl ⇒ insulin 3 units/h*

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

Lepercq J, et al. A standardized protocol to achieve normoglycaemia during labour and delivery in women with type 1 diabetes. Diabet Metab 34;33–37, 2008

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

Preconception Care & Subsequent type1 Diabetic Pregnancies

- to Achieve Optimal Metabolic Control, Without Increased Risk of Maternal Hypoglycemia
- to Prevent Maternal Fetal Adverse Outcomes

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 15, Number 4, 2013

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[1] E. Ansaldi· O. Trifoglio S.Abbruzzese, M. Bongiovanni, M. Agrusta, A.Napoli,

4 Centres

from Western Italy




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.

Experiences of Continuous Subcutaneous Insulin Infusion
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, and A. Napoli, DIABETES TECHNOLOGY & THERAPEUTICSVolume 15, Number 4, 2013

END POINTS

EFFICACY

- Maternal CBG values at TARGET (70–140 mg/dL; 3.8-7.7mMol/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)

Experiences of Continuous Subcutaneous Insulin Infusion in Pregnant Women with Type 1 Diabetes During Delivery from Four Italian Centers: A Retrospective Observational Study
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TABLE 1	Total Sample	CSII	RT-CGM	P[a]
Number	65	47	18	
Age (yrs)	31±5	30.5±5	32±6	NS
D. Duration (yrs)	16±8	15± 8	17±10	NS
Preg. BMI kg/m^2	24±3	25± 4	24±2	NS
Multiparity	31 (48%)	26 (55%)	5 (27%)	NS
PregestationalHbA1c (%)	6.6±1	6.7±1.4	6.3±1	NS
3rd trimester HbA1c(%)	5.9± 2[b]	6.2±1.7	5.2±0.4[c]	<.01
Planned Preg(*n*)	25(38%)	15 (32%)	10 (55%)	NS
Schooling (yrs)	13±3	13±3	13±2	NS

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

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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

Experiences of Continuous Subcutaneous Insulin Infusion in Pregnant Women with Type 1 Diabetes During Delivery from Four Italian Centers: A Retrospective Observational Study
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Experiences of Continuous Subcutaneous Insulin Infusion in Pregnant Women with Type 1 Diabetes During Delivery from Four Italian Centers: A Retrospective Observational Study

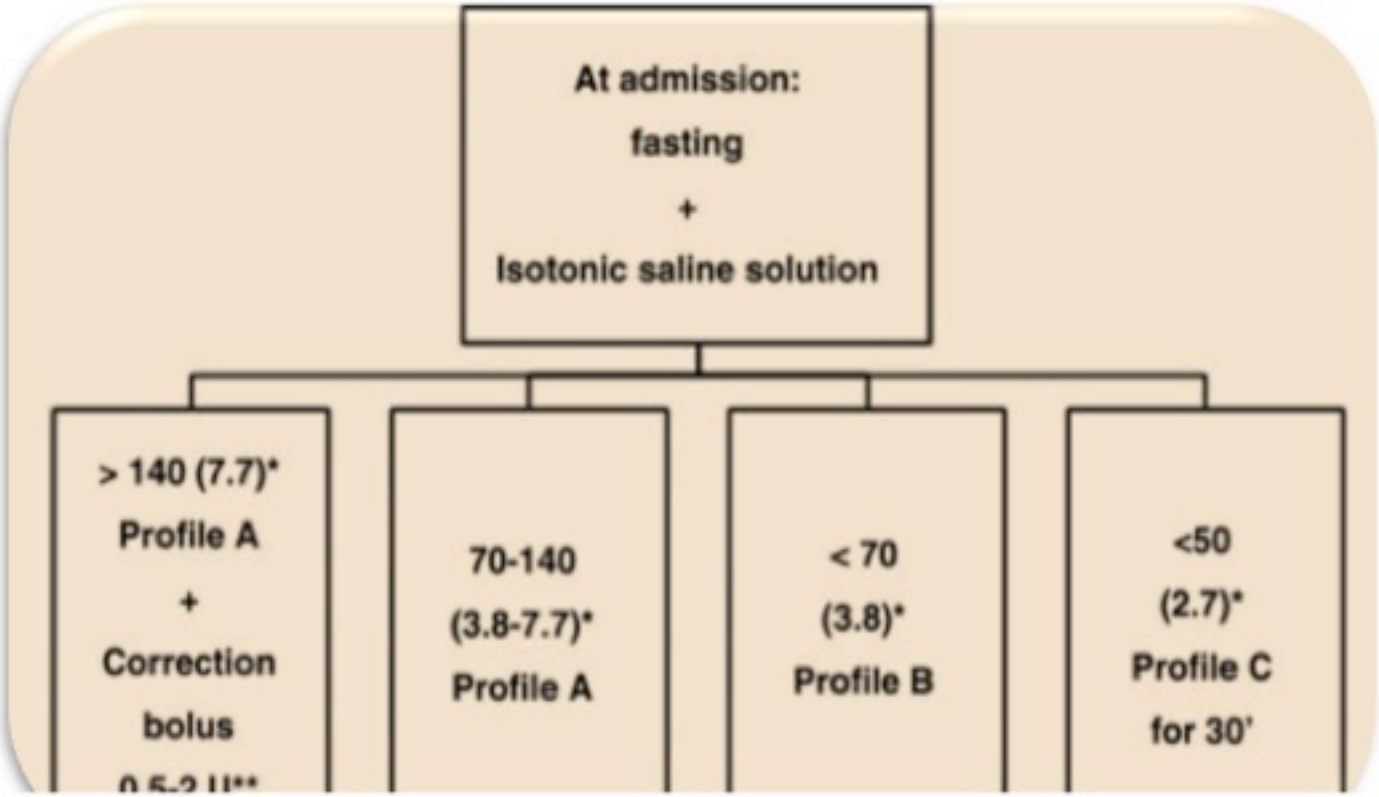
Research Design and Methods

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

PROFILE A	PROFILE B	PROFILE C
Basal Rate in Use	50% Actual Basal Rate	0,1-0,2 U/h (CBG < 70mg/dl)

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

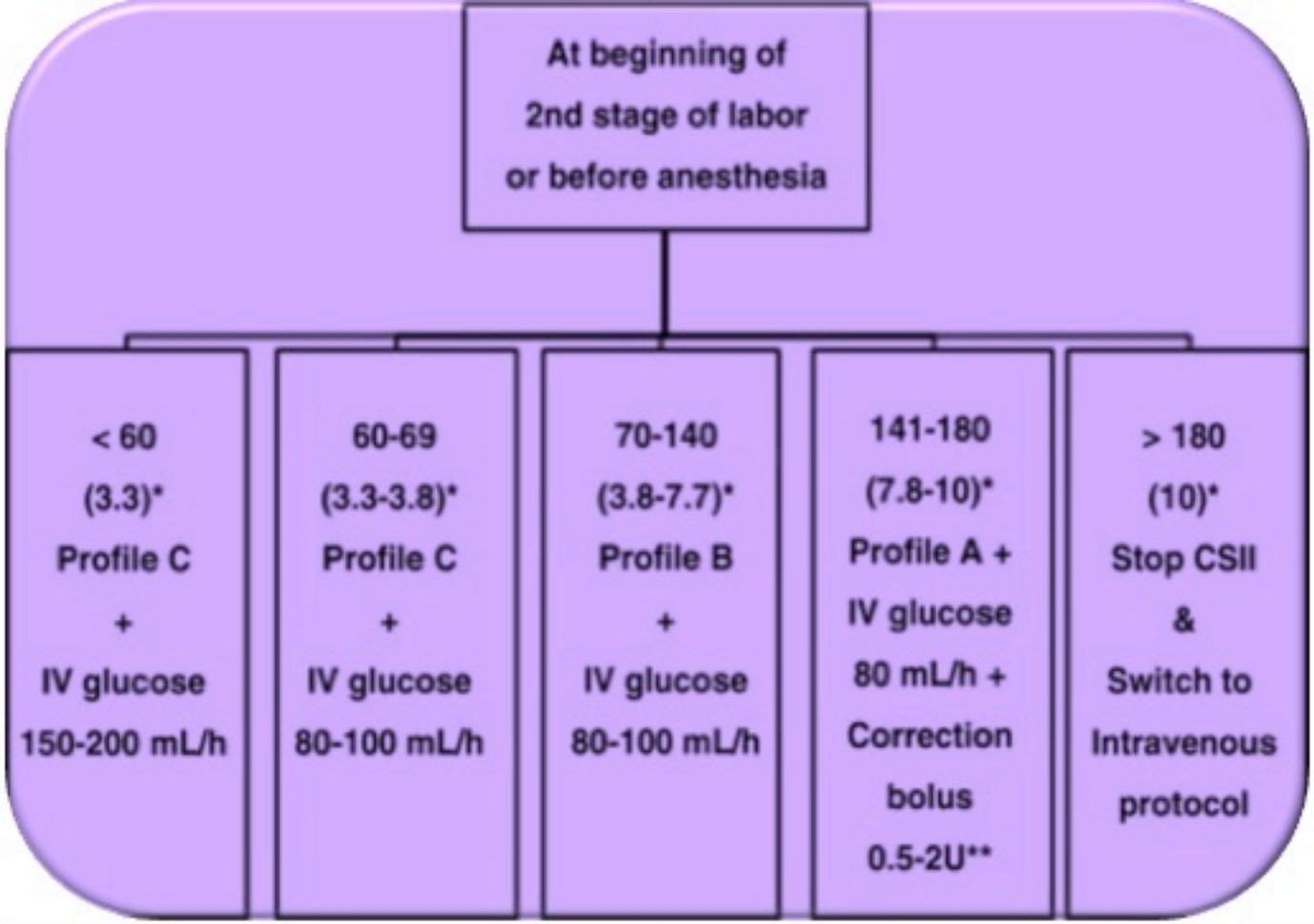
- at the time of Admission in the case of CS or Spontaneous Labor
- 2 h after the Intravaginal Administration of Prostaglandin in Induced labor (IL)

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

PROFILE A	PROFILE B	PROFILE C
Basal Rate in Use	50% of Actual Basal Rate	0,1-0,2 U/h (CBG < 70mg/dl)

Table 3.

C.B.G. values & I.B.R. in Different Modalities & Stages of Delivery

No Differences in Different Delivery Modalities

	Cesarean Section	Spontaneous Labor	Induced Labor
Number of Patients	56	5	4
At Admission			
IBR (U/h)	1.4 ± 0.4	1.3 ± 0.4	1.1 ± 0.3
CBG (mg/dL)	96 ± 24	98 ± 12	92 ± 18
Anesthesia or Second Stage of Labor			
0 min			
IBR (U/h)	1.4 ± 0.4	1.3 ± 0.4	1.1 ± 0.3
CBG (mg/dL)	106 ± 33	77 ± 8	89 ± 19
30 min			
IBR (U/h)	0.6 ± 0.4	0.6 ± 0.3	0.55 ± 0.1
CBG (mg/dL)	109 ± 42	94 ± 17	88 ± 4
60 min			
IBR (U/h)	0.6 ± 0.4	0.4 ± 0.3	0.15 ± 0.1
CBG (mg/dL)	123 ± 49	101 ± 33	86 ± 9

Maternal & Fetal Outcomes:
Impact RT-CGM+CSII vs CSII during Delivery

Basal Rate during Delivery was 0.6 ± 0.4 U/h (PROFILE B)

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

	RT-CGM	CSII-alone group	
0 min	80 ± 14 mg/dL	111 ± 32 mg/dL	($P < 0.01$)
30 min	79 ± 11 mg/dL	109 ± 42 mg/dL	($P < 0.02$)
60 min	98 ± 20 mg/dL	125 ± 51 mg/dL	(*P ns*)

None of the Women switched to IVP

C.B.G. Values & I.B.R. in Peri-Partum Period

	Prepartum	Delivery	24hr after
RTCG+CSII	90	85	122 mg/dl
CSII	114	127	122 mg/dl

C.B.Glucose (mg/dl)

1.3 U/h T0'	0.6 U/h T60'	0.5 U/h 24h

Average Insulin Infusion Rate (U/h)

At ADMISSION PROFILE A

DELIVERY PROFILE B
86% of women

DELIVERY PROFILE C
in 2/5 sl & 4/4il

ORAL FEEDING PROFILE B

Conclusions

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

Safety of CSII

LIMITS

Retrospective
Self Selected Population
No Control Group
Low Number of Vaginal Deliveries

BMC Pregnancy and Childbirth

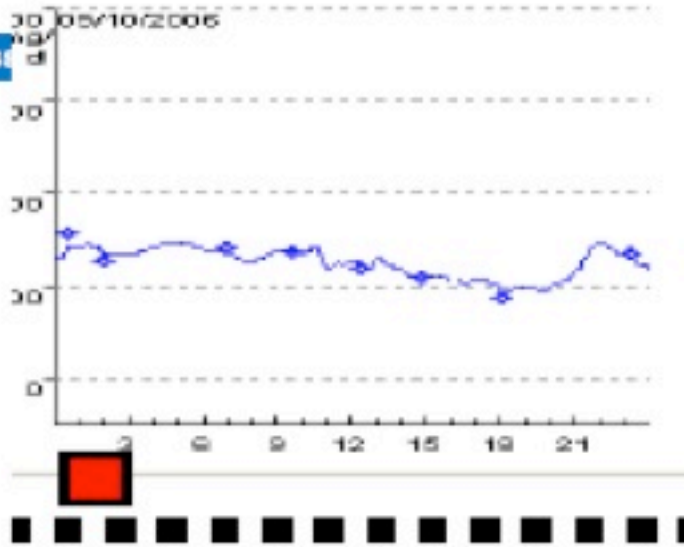
BioMed Central

Technical advance

Open Access

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.

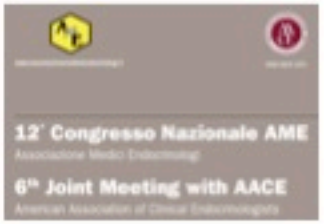
Insulin administered i.v. & the dose was changed on the basis of glycaemia

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.

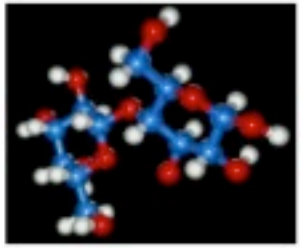
Lactation is Important Variable in this Period of Dynamic Metabolic Changes

Lactating vs	Non Lactating
PRL 8 weeks postpartum with no difference between Type1 Diabetes & Controls	⇑
Estradiol	⇓
Progesterone	⇓
IRI	⇓
AUC IRI after IVGTT	⇓
Insulin sensitivity	⇑
Insulin secretion	⇑
Glucose	⇓
Glucose intolerance	⇓

Am. J. Clin. Nutr. 58. 49-53 1993; OsromKM, Ferris AM 1993

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 ⇩ increased less at 3 years in women who had lactated at least 3 months compared with parous women who never lactated

Gunderson E.P. et al, Obstet Gynecol. 2007

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.

Ram KT, et al, Am. J. Obstet. Gynecol. 2008

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

	Lactating n=404	Not-Lactating n=405	*p*
AUC-G (g.min/dl)	17.0±4.2	17.9±5.0	*.01*
Fasting Glucose (mg/dl)	93±13	98±17	*.0001*
2-hr Glucose (mg/dl)	124±41	134±49	*.o1*
Diabetes Mellitus	17 (4,2%)	38 (9,4%)	*.01*
Cholesterol (mg/dl)	219±42	213±42	*ns*
HDL (mg/dl)	48±11	44±10	*<.01*
LDL (mg/dl)	136±35	131±35	*ns*
Triglycerides(mg/dl)	182±175	198±125	*ns*

S. Kjos, et al
Obstetrics and Gynecology, 1993

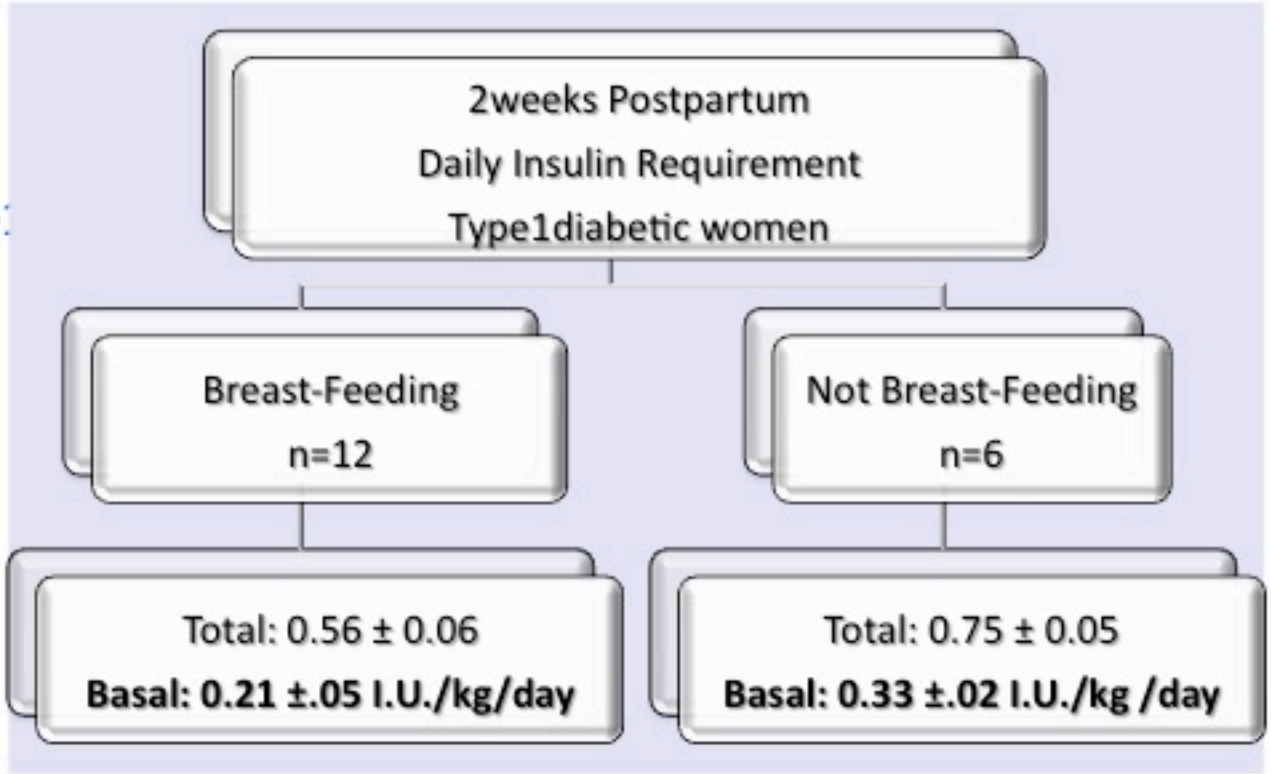
Breast-feeding in Pregestational Diabetic Women

Success of Breastfeeding is not associated with

- Diabetes-related parameters: diabetes duration or metabolic control.
- Route of delivery
- Parity
- Neonatal weight

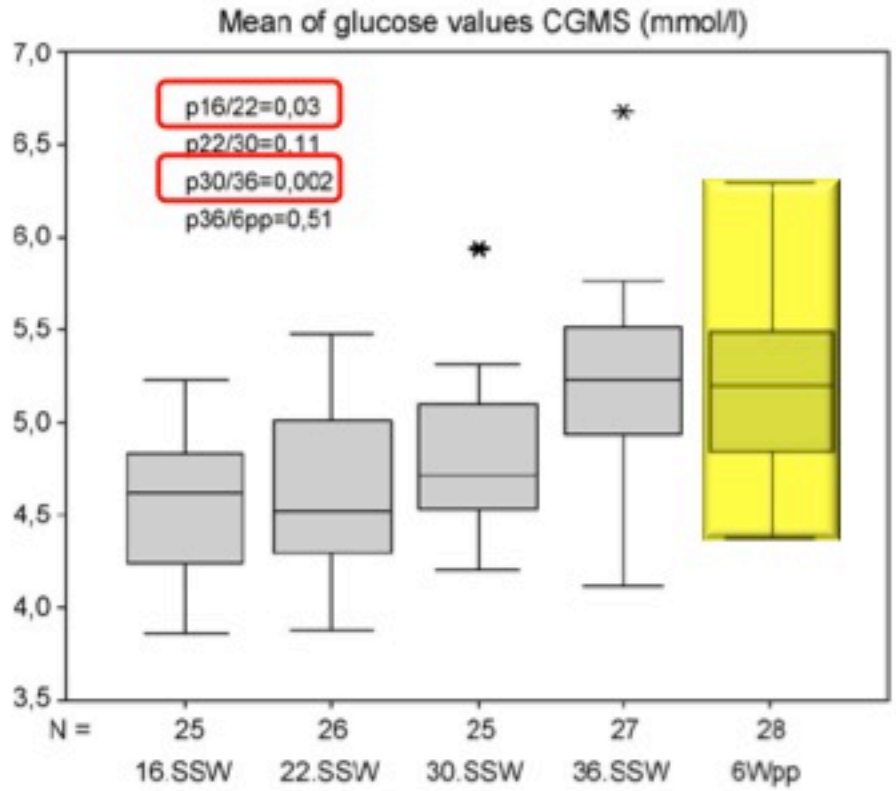
Concerns

Frequent hypos in type1



Riviello et al.
Breastfeeding and Insulin, Endocr Pract. 2009

Continuous Glucose Monitoring in Healthy Women

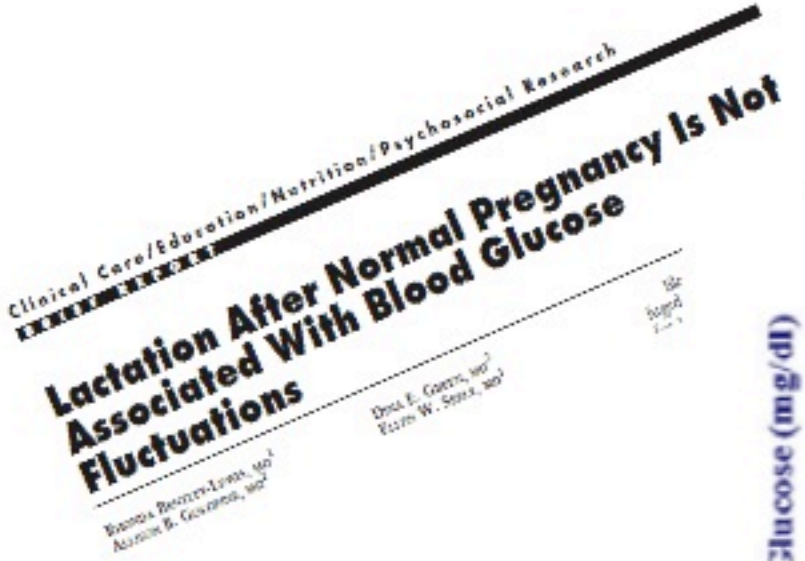


Mean Blood Glucose Levels
of the 16th, 22nd, 30th weeks of gestation showed a tendency to increase, significantly higher in the 36th week.

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

T.Siegmud et al. E.J.O.G, 2008


Clinical Care/Education/Nutrition/Psychosocial Research

Lactation After Normal Pregnancy Is Not Associated With Blood Glucose Fluctuations

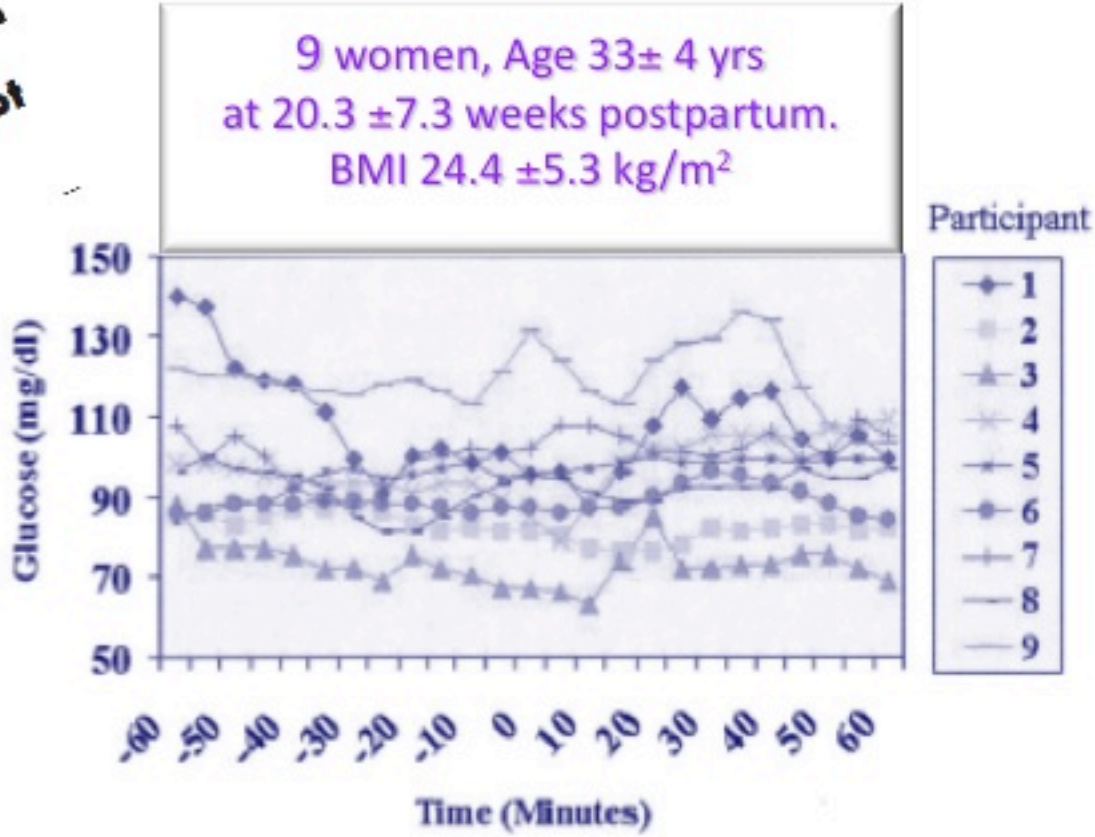


Figure 1—*Blood glucose levels (mg/dl) collected every 5 min during the 60 min before and after the start of lactation (time = 0) for each of the nine participants in the study.*

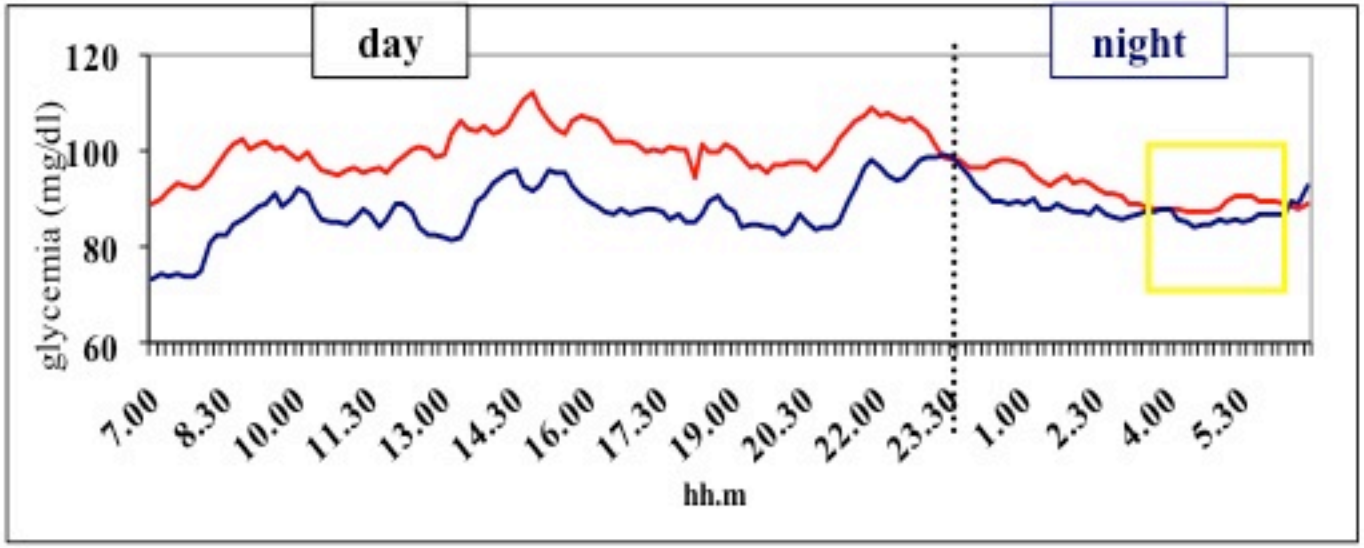
1hr- before vs 1hr- after lactation:
Mean BG :
95±14 vs. 96±15 mg/dl, *p .9*
AUCg:
376.9±53.3 vs. 382.8±56.9 mg, *p .34*

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

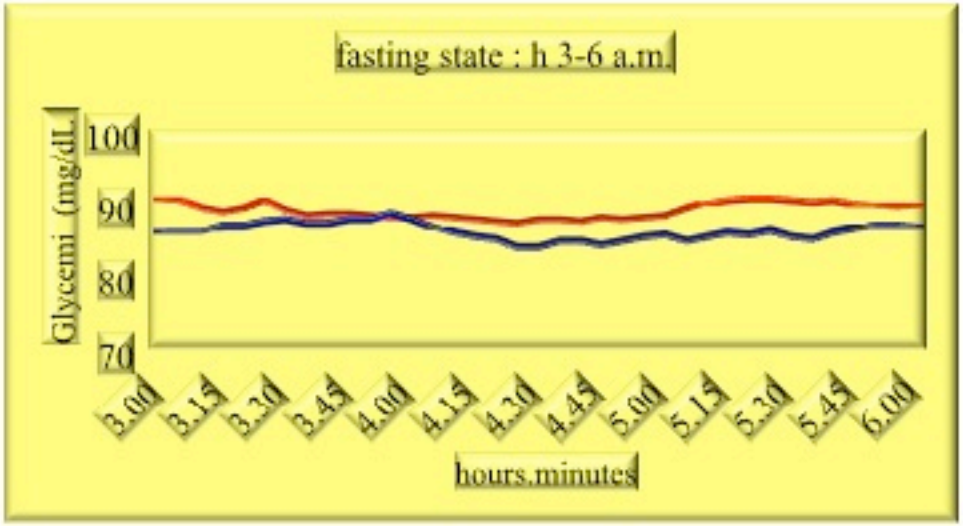
Continuous Glucose Monitoring in prior-GDM

CGM during Breast-Feeding in Normotolerant Women (OGTT-) With & Without Previous GDM



Prior-GDM/normotolerant at follow-up

Normotolerant in & out of pregnancy



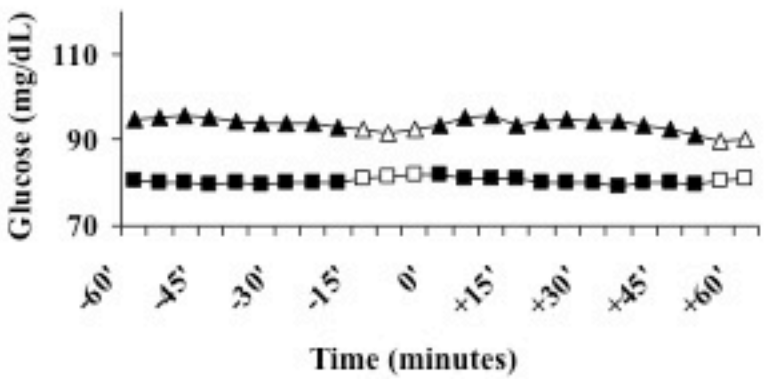
CGM during Breast-Feeding: Comparison between studies

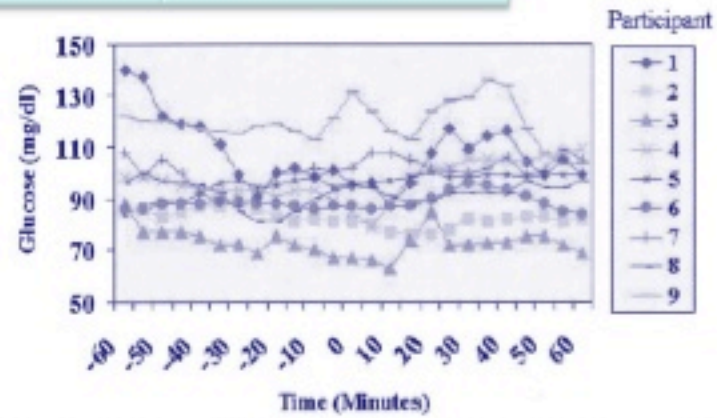
Comparison	T. Siegmud 2008 n.a. n=28	Colatrella, Napoli Breast-feeding N/N □ n=15	Colatrella, Napoli Breast-feeding PriorGDM/N ▲ n=18
Age (yr)	29.6 ± 4.5	36.2 ± 3.4	35.2 ± 4.0
72h CGM (mg/dL)	93.7 ± 9.0	87.5 ± 8.7	*101.4 ± 14.2
Daytime	n.a.	89.0 ± 9.2	*99.4 ± 10.5
Night-time	n.a.	84.8 ± 9.5	*N/N vs pGDM/N: significant 93.0 ± 14.2

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

CGM during sukling: Comparison between studies

Comparison	Bentley n=9	Colatrella, Napoli N/N □ n=15	Colatrella, Napoli PriorGDM/N ▲ n=18
Age (yr)	33 ± 4	36.2 ± 3.4	35.2 ± 4.0
Weeks after delivery	20,3 ± 7,3	13.1 ± 5.1	11.5 ± 3.7
BMI(Kg/m$^{2)}$	24,4 ±5,3	23.0 ± 1.6	* 25.9 ± 4.5
60' pre-suckling glucose levels (mg/dL)	95.0 ± 14	80.4 ± 15.6	93.9 ± 15.7
60' post-suckling glucose levels (mg/dL)	96± 15	80.3 ± 13.5	93.2 ± 14.5





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Tante Grazie
Angela Napoli
SAPIENZA