Il dr. Matteo Bonomo dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Medtronic
- Roche
- Menarini

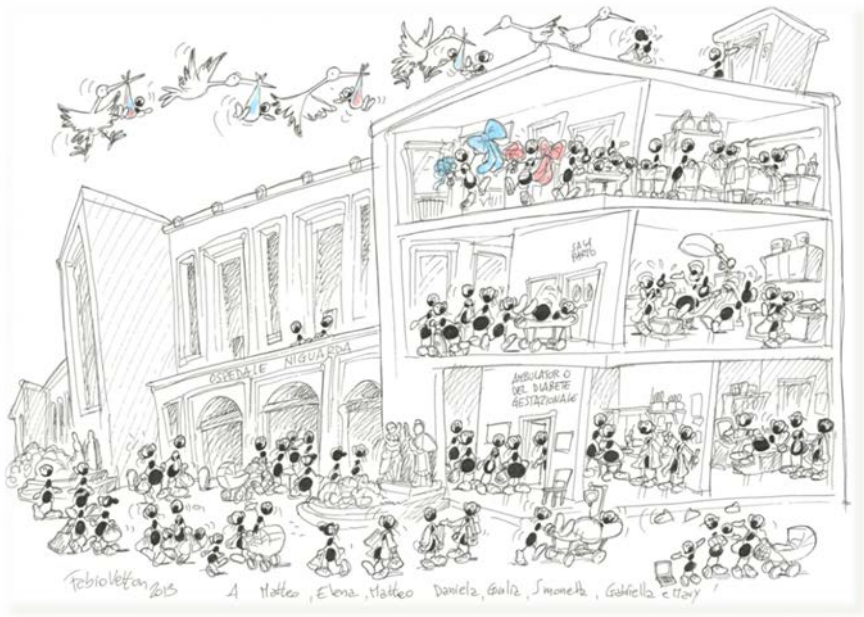
*Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).*

IL DIABETE IN GRAVIDANZA
DALLA RICERCA ALLA PRATICA CLINICA
Chieti, 20 aprile 2018

# LO STUDIO CONCEPTT


**Matteo Bonomo**

CENTRO INTERDISCIPLINARE «DIABETE E GRAVIDANZA»
A.S.S.T. «Grande Ospedale Metropolitano Niguarda",
Milano




ORIGINAL ARTICLE

# The Effect of Real-Time Continuous Glucose Monitoring in Pregnant Women With Diabetes

## A randomized controlled trial

ANNA L. SECHER, MD[1,2,3]
LENE RINGHOLM, MD, PHD[1,2]
HENRIK U. ANDERSEN, MD, DMSC[4]
PETER DAMM, MD, DMSC[1,3,5]
ELISABETH R. MATHIESEN, MD, DMSC[1,2,3]

**OBJECTIVE**—To assess whether intermittent real-time continuous glucose monitoring (CGM) improves glycemic control and pregnancy outcome in unselected women with pregestational diabetes.

**RESEARCH DESIGN AND METHODS**—A total of 123 women with type 1 diabetes and 31 women with type 2 diabetes were randomized to use real-time CGM for 6 days at 8, 12, 21, 27, and 33 weeks in addition to routine care, including self-monitored plasma glucose seven times daily, or routine care only. To optimize glycemic control, real-time CGM readings were evaluated by a diabetes caregiver. $HbA_{1c}$, self-monitored plasma glucose, severe hypoglycemia, and pregnancy outcomes were recorded, with large-for-gestational-age infants as the primary outcome.

**RESULTS**—Women assigned to real-time CGM ($n = 79$) had baseline $HbA_{1c}$ similar to that of women in the control arm ($n = 75$) (median 6.6 [range 5.3–10.0] vs. 6.8% [5.3–10.7]; $P = 0.67$) (49 [34–86] vs. 51 mmol/mol [34–93]). Forty-nine (64%) women used real-time CGM per protocol. At 33 weeks, $HbA_{1c}$ (6.1 [5.1–7.8] vs. 6.1% [4.8–8.2]; $P = 0.39$) (43 [32–62] vs. 43 mmol/mol [29–66]) and self-monitored plasma glucose (6.2 [4.7–7.9] vs. 6.2 mmol/L [4.9–7.9]; $P = 0.64$) were comparable regardless of real-time CGM use, and a similar fraction of women had experienced severe hypoglycemia (16 vs. 16%; $P = 0.91$). The prevalence of large-for-gestational-age infants (45 vs. 34%; $P = 0.19$) and other perinatal outcomes were comparable between the arms.

**CONCLUSIONS**—In this randomized trial, intermittent use of real-time CGM in pregnancy, in addition to self-monitored plasma glucose seven times daily, did not improve glycemic control or pregnancy outcome in women with pregestational diabetes.




*Diabetes Care* 36:1877–1883, 2013

# RISULTATI NON MOLTO INCORAGGIANTI?




## Continuous Glucose Monitoring in Pregnancy: We Have the Technology but Not All the Answers

DIABETES CARE, VOLUME 36, JULY 2013

HELEN R. MURPHY

COMMENTARY (SEE SECHER ET AL., P. 1877)

- ✓ For clinicians hoping that CGM may help to improve maternal/fetal outcomes, the **current results are disappointing.**
- ✓ Acceptance of, and compliance with, CGM in unselected pregnant women was poor. It is also possible that **intermittent use of real-time CGM is not beneficial.**
- ✓ Clearly, more data are required before routine clinical use of CGM in pregnancy can be fully endorsed.

# TECNOLOGIA E DIABETE IN GRAVIDANZA OSTACOLI ALLA VALUTAZIONE EBM

- **Problematiche di tipo etico**
- **Continua e rapida evoluzione della materia di studio**
- **Impossibilità ad effettuare studi in cieco**
- **Limiti di una randomizzazione rigida**

# UNO STUDIO NECESSARIO




## Continuous Glucose Monitoring in Pregnancy: We Have the Technology but Not All the Answers

DIABETES CARE, VOLUME 36, JULY 2013

HELEN R. MURPHY

COMMENTARY (SEE SECHER ET AL., P. 1877)

- **An international trial on Continuous Glucose Monitoring In Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) will now evaluate the role of continuous real-time CGM before and during pregnancy. It is not the devices per se but how patients, their spouses/significant others, and health professionals interact with CGM that will likely determine outcomes.**

# Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial

CONCEPTT

Co-Principal Investigators:
Dr Denice Feig, Canada & Prof Helen Murphy, UK

JDRF

Canadian Clinical Trial Network
Accelerating Diabetes Breakthroughs

NHS National Institute for Health Research

# CONCEPTT



## Lei ha il Diabete di Tipo 1?

- E' in gravidanza o sta programmando una gravidanza?

In tal caso Lei potrebbe essere considerata per partecipare a questo studio di ricerca internazionale!

CONCEPTT è uno studio che mette a confronto gli effetti dell'aggiunta del Monitoraggio Continuo del Glucosio ("Continuous Glucose Monitoring, CGM") alla terapia standard rispetto alla sola terapia standard, in donne che sono in gravidanza o che stanno programmando una gravidanza.


Principal Investigator: **Dr. Denice Feig**, Mount Sinai Hospital

**CONCEPTT Coordinating Center**
The Centre for Mother, Infant, and Child Research (CMICR)
Sunnybrook Research Institute
C8-2075 Bayview Avenue |Toronto, ON |M4N 3M5
Email: conceptt@sunnybrook.ca
Website: www.conceptt.ca


Per maggiori informazioni riguardo allo studio CONCEPTT, La preghiamo di contattare il coordinatore locale al seguente recapito:


**Sponsored by:**

JDRF · Canadian Clinical Trial Network · Accelerating Diabetes Breakthroughs · MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex · Sunnybrook Research Institute




# UNO STUDIO JDRF

**Obiettivo principale**

**Valutare se l'uso del RTCG (associato a CSII o MDI) può migliorare il controllo glicemico in donne con DMT1 con gravidanza in atto o in programmazione senza comportare un aumento dell'occorrenza di ipoglicemia.**

# Continuous glucose monitor



CONCEPTT

# Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial

## INTERNATIONAL CENTRES

**Enrollment is expected to include 110 women with type 1 diabetes who are planning pregnancy and approximately 214 women with type 1 diabetes who are pregnant**

**CANADA**
- Alberta Health Services
- Mount Sinai Hospital
- St Joseph's Health Care
- St Michael's Hospital
- Sunnybrook Health Sciences Centre
- The Ottawa Hospital

**ITALY**
- **Milano Niguarda Ca'Granda Hospital**

**ISRAEL**
- Rabin Medical Center

**SPAIN**
- Hospital De La Santa Creu I Saint Paul

**UNITED KINGDOM**
- Addenbrookes Hospital
- Ipswich Hospital NHS Trust
- King's College London
- Norfolk and Norwich University Hospital

**UNITED STATES OF AMERICA**
- Sansum Diabetes Research Institute

# DISEGNO DELLO STUDIO

- **2 studi randomizzati controllati paralleli:**
  - **In programmazione di gravidanza**
  - **In gravidanza**
- **Multi-centrico: 14 centri, 6 Paesi: UK, Canada, Spagna, Italia, Irlanda, USA**
- **In aperto**
- **Intention-to-treat**

# CRITERI DI INCLUSIONE

- Diagnosi di DMT1 da almeno 1 anno
- Età 18-40 anni
- In terapia con CSII o MDI
- Controllo glicemico non ottimale
  - Inizio gravidanza  HbA1c 6.5-10%, (48-86 mmol/mol)
  - In programmazione HbA1c 7-10% (53-86 mmol/mol)
- Primo trimestre di gestazione  (< 14 settimane)
- Feto unico, vitale, con conferma ecografica

# GRUPPI CGM E CONTROLLO: ELEMENTI COMUNI

- **Visite programmate:**
  - **In gravidanza alle settimane 12, 16, 20, 24, 28, 32, 34, 36, con assistenza ostetrica standard**
  - **In programmazione alle settimane 4, 8, 12, 16, 20 e 24 post-randomizzazione**
- **Target glicemico: 65- 140 mg/dL**
- **Target HbA1c:**
  - **In gravidanza <48 mmol/mol (<6.5%)**
  - **In programmazione<53 mmol/mol (<7.0%)**

# GRUPPO CGM

- **Addestramento all'uso dello strumento, compresa la calibrazione**
- **Consegna di algoritmi sull'adeguamento della dose di insulina**
- **Istruzione a praticare misurazioni su sangue capillare, prima di prendere decisioni terapeutiche**
- **Verifica sulla tecnica di applicazione del sensore**
- **Controlli per reazioni cutanee**

# GRUPPO DI CONTROLLO

- **Effettuazione di almeno 7 misurazioni capillari ogni giorno**
- **Consegna di algoritmi sull'adeguamento della dose di insulina**
- **Effettuazione monitoraggio CGM criptato**
  - **In gravidanza: alla settimana 24 e 34 di gestazione**
  - **In programmazione: alla settimana 12 e 24**

# STUDIO GRAVIDANZA
# DATI MATERNI AL BOOKING

| | CGM N=108 | Controlli N=107 |
|---|---|---|
| Età anagrafica (aa) | 31.4±4.5 | 31.5±4.9 |
| Origine europea | 87.0% | 84.1% |
| Età gestazionale (sett.) | 10.5±2.2 | 11.0±2.0 |
| Durata del diabete (aa) | 17.0 (6.0-28.0) | 16.0 (6.6-26.4) |
| BMI (kg/m2) | 26.1±5.1 | 25.3±3.8 |
| Acido folico pre-concepimento | 50.5% | 51.4% |
| Terapia insulinica<br>CSII<br>MDI | <br>46.3%<br>53.7% | <br>44.9%<br>55.1% |
| Dose insulinica totale (U/kg/24 h) | 0.69±0.25 | 0.76±0.31 |

CONCEPTT

September 2016

# CONCEPTT



## INVESTIGATOR MEETING ANNOUNCEMENT



CONCEPTT will be hosting a meeting to present the primary results on:

***April 27 & 28, 2017, Milan, Italy***

Invitations will be sent shortly


CONCEPTT

EASD 2017
Lisbon – Portugal

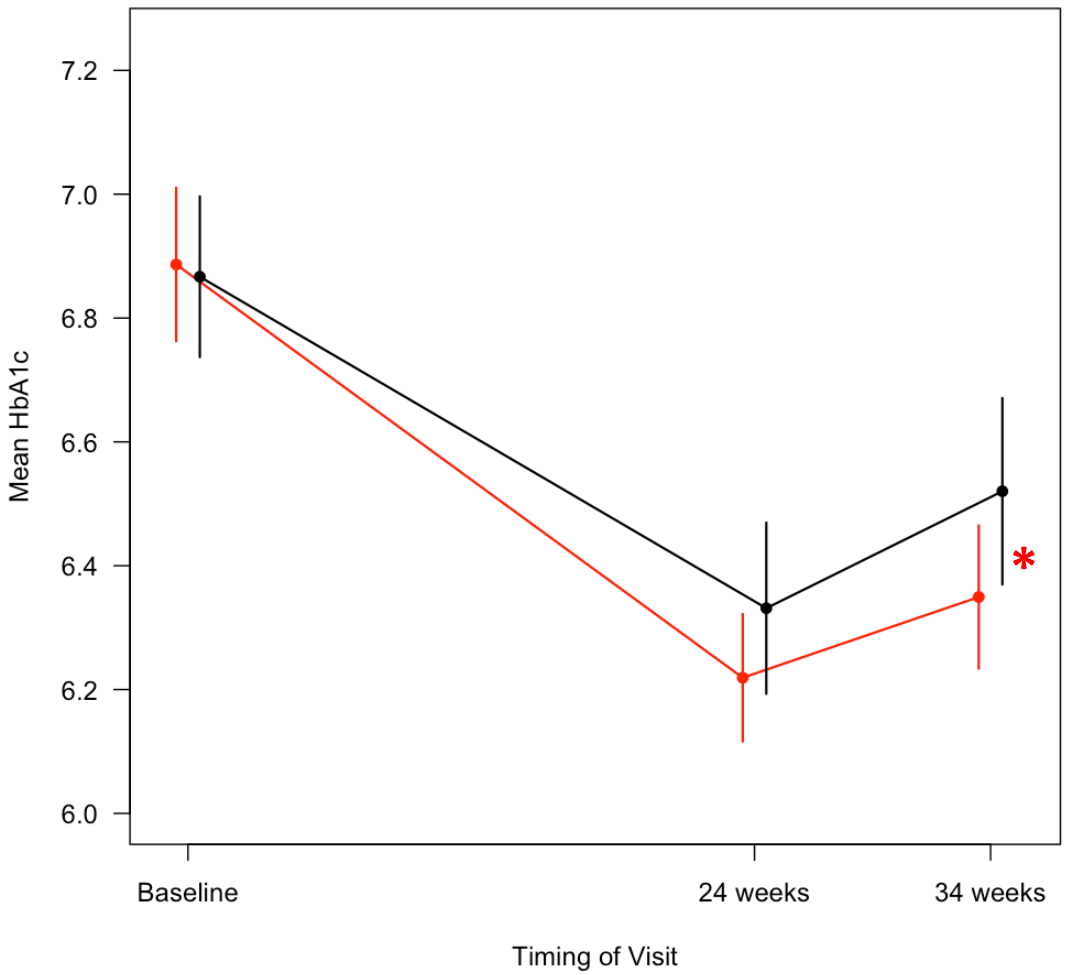
53rd Annual Meeting of the European Association for the Study of Diabetes

11 - 15 September 2017

# RISULTATI CONTROLLO GLICEMICO



# HbA1c (OUTCOME PRIMARIO) - GRAVIDE




- CGM
- CONTROLLI

**Imputazione multipla dei dati mancanti**

**Missing:**
**18 CGM e 23 Controlli**

**Simile il risultato sui dati disponibili**

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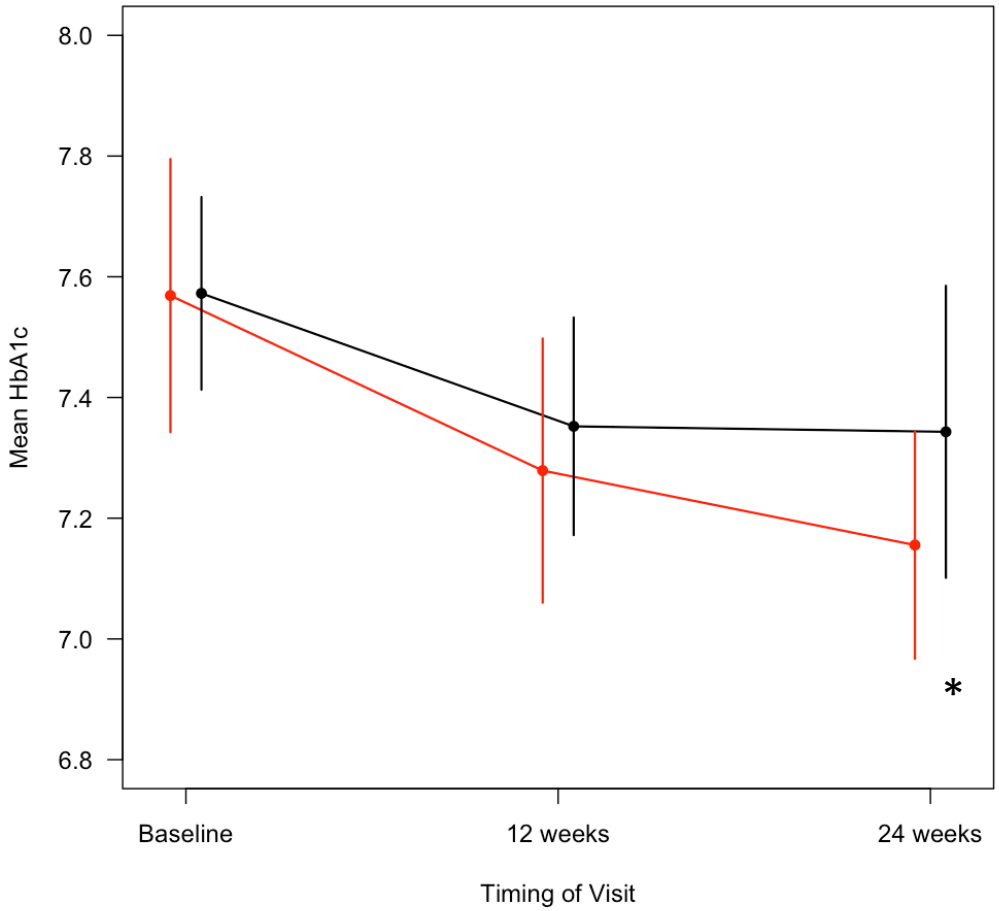
***mean difference -0.19%; 95% CI -0.34—0.03; p = 0.0207**

# OUTCOMES GLICEMICI SECONDARI

| | Basale | | Settimana 34 | | |
|---|---|---|---|---|---|
| | CGM N=107 | Controlli N=107 | CGM N=103 | Controlli N=104 | P-value |
| # Donne con ipo gravi | 7 (6.5%) | 4 (3.7%) | 11 (10.7%) | 12 (11.5%) | 1.0 |
| # Episodi ipo gravi | 11 | 5 | 18 | 21 | |
| DKA | N/A | N/A | 2 (1.9%) | 2 (1.9%) | 1.0 |
| Passate a CSII | | | 1 (1.0%) | 3 (2.9% ) | 0.62 |
| Dose insulinica totale (U/kg/24 h) | 0.69±0.25 | 0.76±0.31 | 0.99±0.41 | 1.07±0.42 | 0.14 |

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# HbA1c (PROGRAMMAZIONE)




- CGM
- CONTROLLI

***mean difference -0.17%; 95% CI -0.43—0.09; p = 0.20**

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# DATI CGM GRAVIDANZA



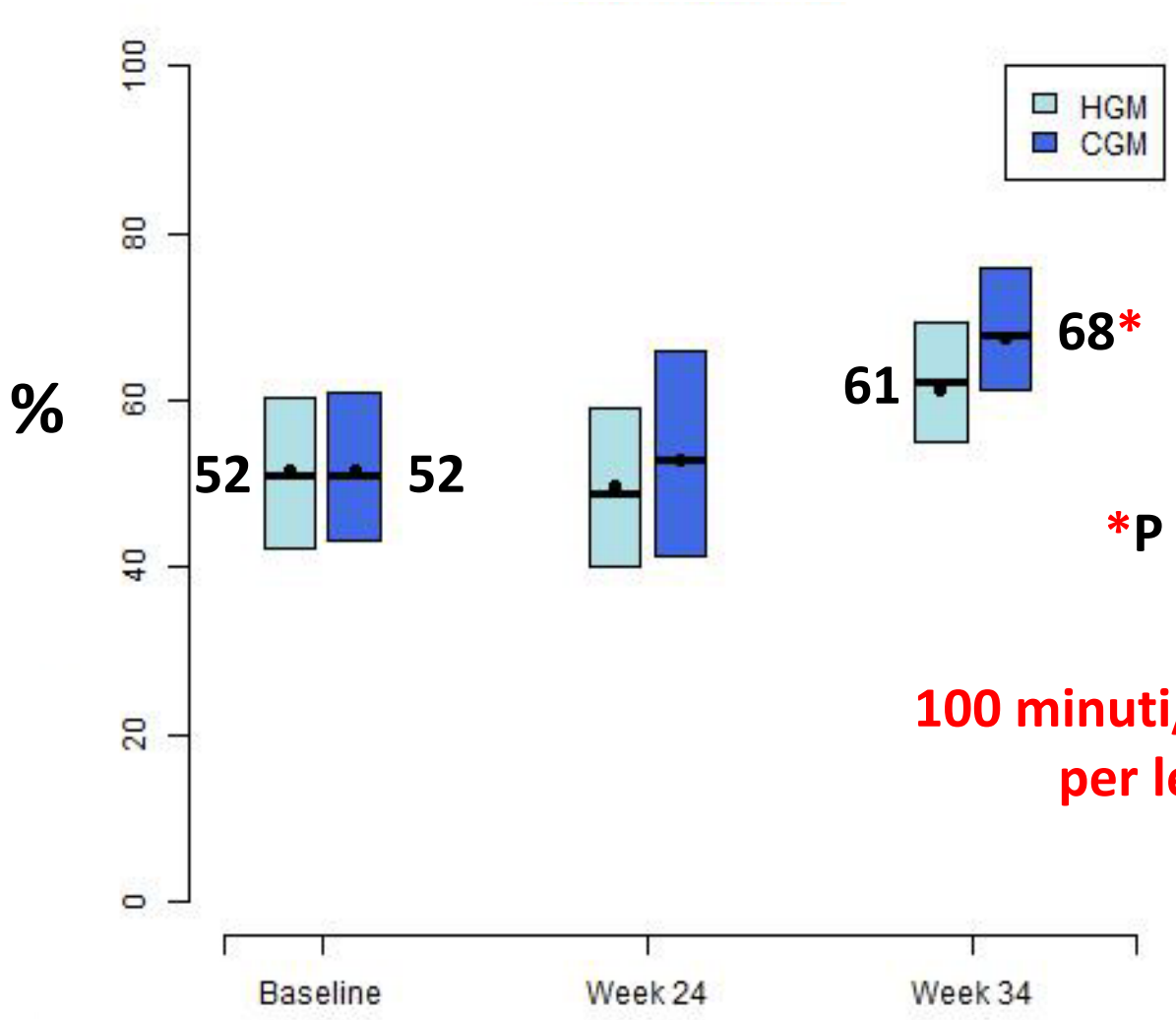
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# GRUPPO CGM IN GRAVIDANZA – USO SENSORE

| | totale | ≤24 sett. | 25-34 sett. |
|---|---|---|---|
| | N=108 | N=108 | N=108 |
| **Mediana (25°, 75° percentile)** | 6.1 (4.0, 6.8) | 6.0 (4.0, 6.7) | 6.5 (3.9, 7.0) |
| **<6 gg** | 45% | 49% | 44% |
| **≥6 gg** | 55% | 55 51% | 56% |

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# DATI CGM PROGRAMMATI – GRAVIDANZA
# TEMPO IN RANGE 65-140 mg/dL



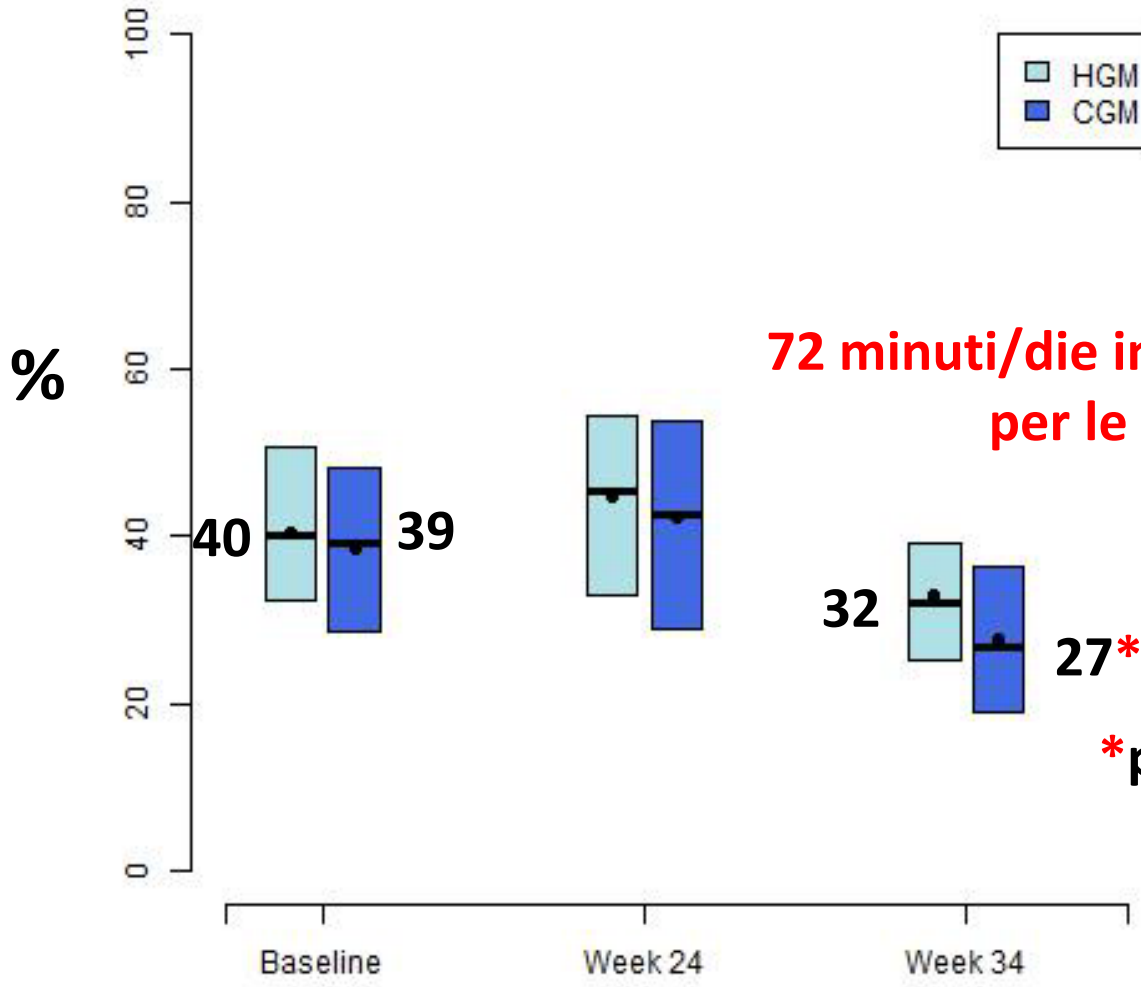

*P = 0.003

**100 minuti/die in più in range per le donne CGM**

Pump = Pens
N=31 sites

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# DATI CGM PROGRAMMATI – GRAVIDANZA
# TEMPO IN IPER >140 mg/dL



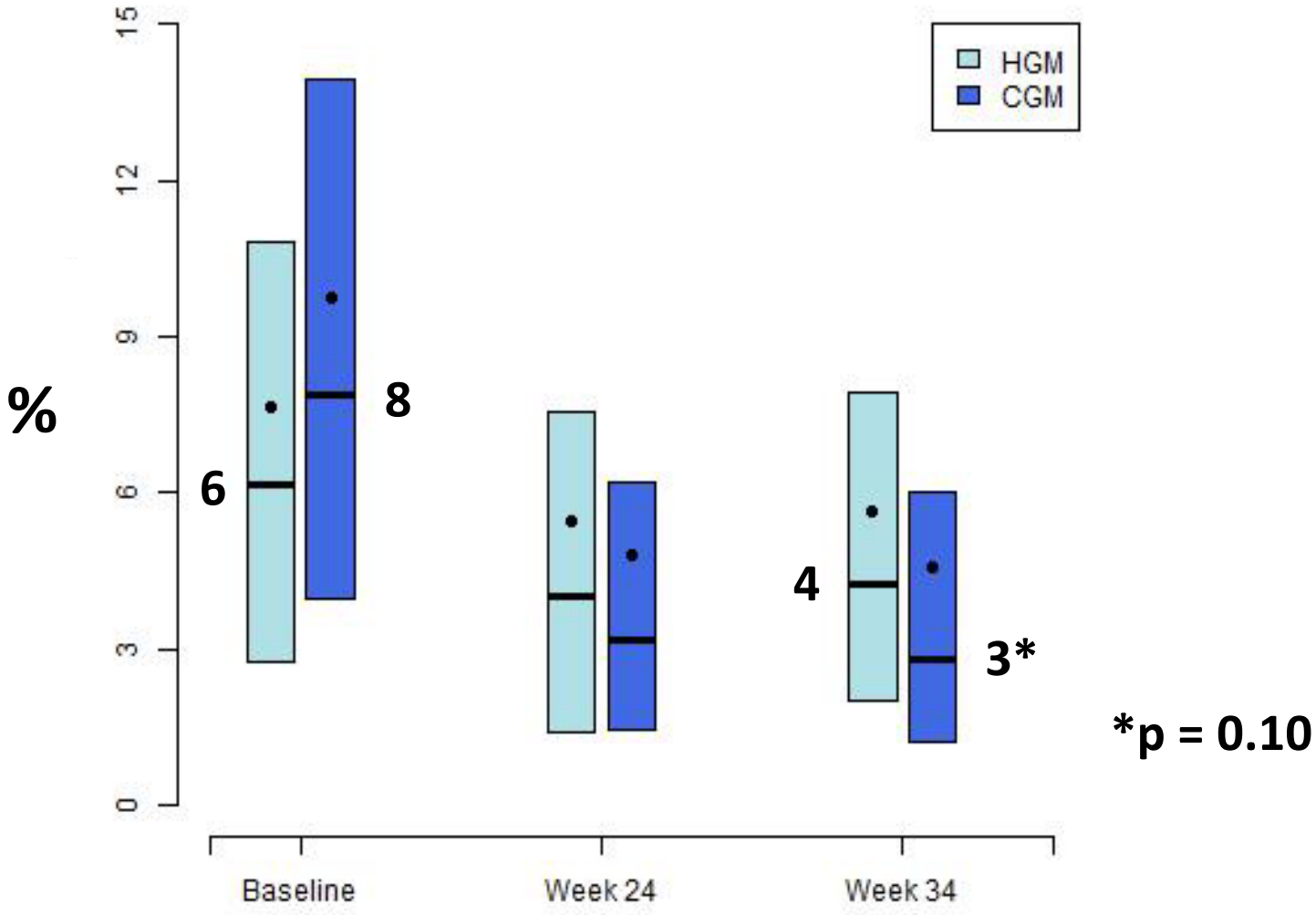

**72 minuti/die in meno sopra il range per le donne CGM**

***p = 0.028**

Pump = Pens
N=31 sites

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# DATI CGM PROGRAMMATI – GRAVIDANZA
# TEMPO IN IPO <65 mg/dL




*p = 0.10

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# DATI CGM PROGRAMMATI – GRAVIDANZA VARIABILITA' GLICEMICA

| | Basale | | Settimana 34 | | |
|---|---|---|---|---|---|
| | CGM N=107 | Controlli N=107 | CGM N=77 | Controlli N=77 | P-value |
| **CV (%)** | 42 (38-47) | 42 (36-47) | 32 (28-37) | 34 (29-39) | 0.058 |
| **SD (mmol/L)** | 3.1 (2.6-3.6) | 3.1 (2.6-3.8) | 2.2 (1.8-2.5) | 2.4 (2.0-2.8) | **0.0359** |
| **MAGE (mmol/L)** | 6.0 (5.1-7.1) | 6.4 (5.5-7.8) | 4.2 (3.5-4.9) | 4.6 (3.9-6.0) | **0.0455** |
| **Variazione (mmol/L/h)** | 2.1 (1.9-2.5) | 2.2 (1.9-2.5) | 2.0 (1.7-2.3) | 1.6 (1.3-2.0) | **<0.0001** |

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# PROBLEMI CON L'USO DEL CGM

## STRUMENTALI

| Tutti | 80.6% |
|---|---|
| Problemi di connessione | 33% |
| Difettosa  inserzione | 24% |
| Sanguinamento in inserzione | 28% |
| Distacco accidentale sensore | 19% |
| Rimozione per intolleranza | 17% |
| Perdita funzione anticipata | 26% |
| Altro | 49% |

## CUTANEI

| Tutti | 47.6% |
|---|---|
| Eritema acuto | 29% |
| Edema acuto | 0% |
| Prurito cronico | 4% |
| Cute secca | 8% |
| Ipopigmentazione | 1% |
| Iperpigmentazione | 6% |
| Altro | 27% |

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# ESITI OSTETRICI E NEONATALI



# ESITI SFAVOREVOLI GRAVI

| | CGM N=105 | Controlli N=106 |
|---|---|---|
| **Aborti spontanei <20 sett.** | 5 (4.8%) | 4 (3.8%) |
| **MEF** | 0 | 1 |
| **IVG** | 0 | 1 |
| **Malformazioni congenite§** | 2 | 3 |

§ Stenosi aortica e ipospadia di grado 1 (gruppo CGM)
Sindrome cuore destro ipoplastico (IVG), arteria succlavia destra aberrante, idronefrosi bilaterale (gruppo controllo)

# ESITI OSTETRICI a)

| | CGM N=100 | Controlli N=102 | P-value |
|---|---|---|---|
| Disordini ipertensivi | 18.0% | 27.4% | 0.13 |
| Cronici, peggioramento | 2.0% | 3.9% | 0.68 |
| Gestazionali | 8.0% | 8.8% | 1.0 |
| Preeclampsia | 9.0% | 17.6% | 0.10 |
| T.C. | 63.0% | 72.5% | 0.18 |
| Aumento ponderale materno (kg)‡ | | | |
| Alla 34a settimana | 13.1 | 13.7 | 0.22 |
| Sett. 16-34 | 8.9 | 9.7 | 0.09 |
| Degenza Ostetricia (gg) | 3.5 | 4.2 | 0.10 |

‡Peso iniziale dichiarato e/o registrato come pre-gravidanza. Misurato direttamente il peso fra la 16a e la 34a sett.

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# ESITI OSTETRICI b)

| | CGM | Control | P-value |
|---|---|---|---|
| | N=100 | N=102 | |
| Epoca gestazionale (Mediana) | 37.4 | 37.3 | 0.50 |
| Pretermine <37 sett. | 38.0% | 42.2% | 0.57 |
| Pretermine <34 sett. | 5.0% | 10.8% | 0.19 |

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# ESITI NEONATALI

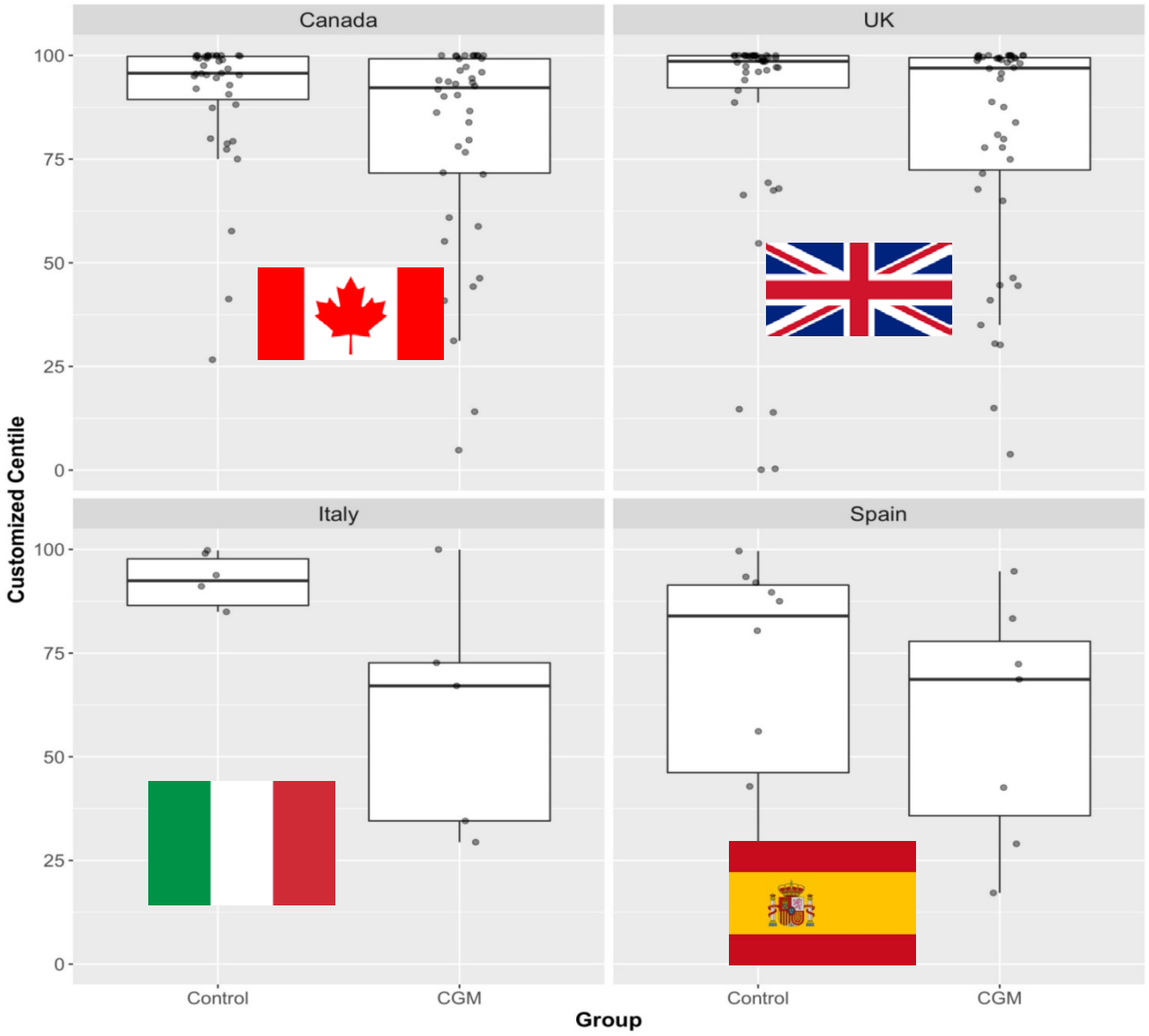
| | CGM N=100 | Controlli N=100 | P-value |
|---|---|---|---|
| Peso alla nascita (g) | 3545.4±649 | 3582.5±777 | 0.37 |
| Mediana centile◊ | 92 (68-99) | 96 (84-100) | 0.049 |
| LGA >90° centile | 53.0% | 69.0% | **0.021** |
| Estremo LGA >97.7° centile | 36.0% | 44.0% | 0.31 |
| Macrosomia ≥4000g | 23.0% | 27.0% | 0.62 |
| SGA <10° centile | 2.0% | 2.0% | 1.0 |

**LGA Odds ratio 0.51; 95%CI 0.28—0.90, p=0.0210**

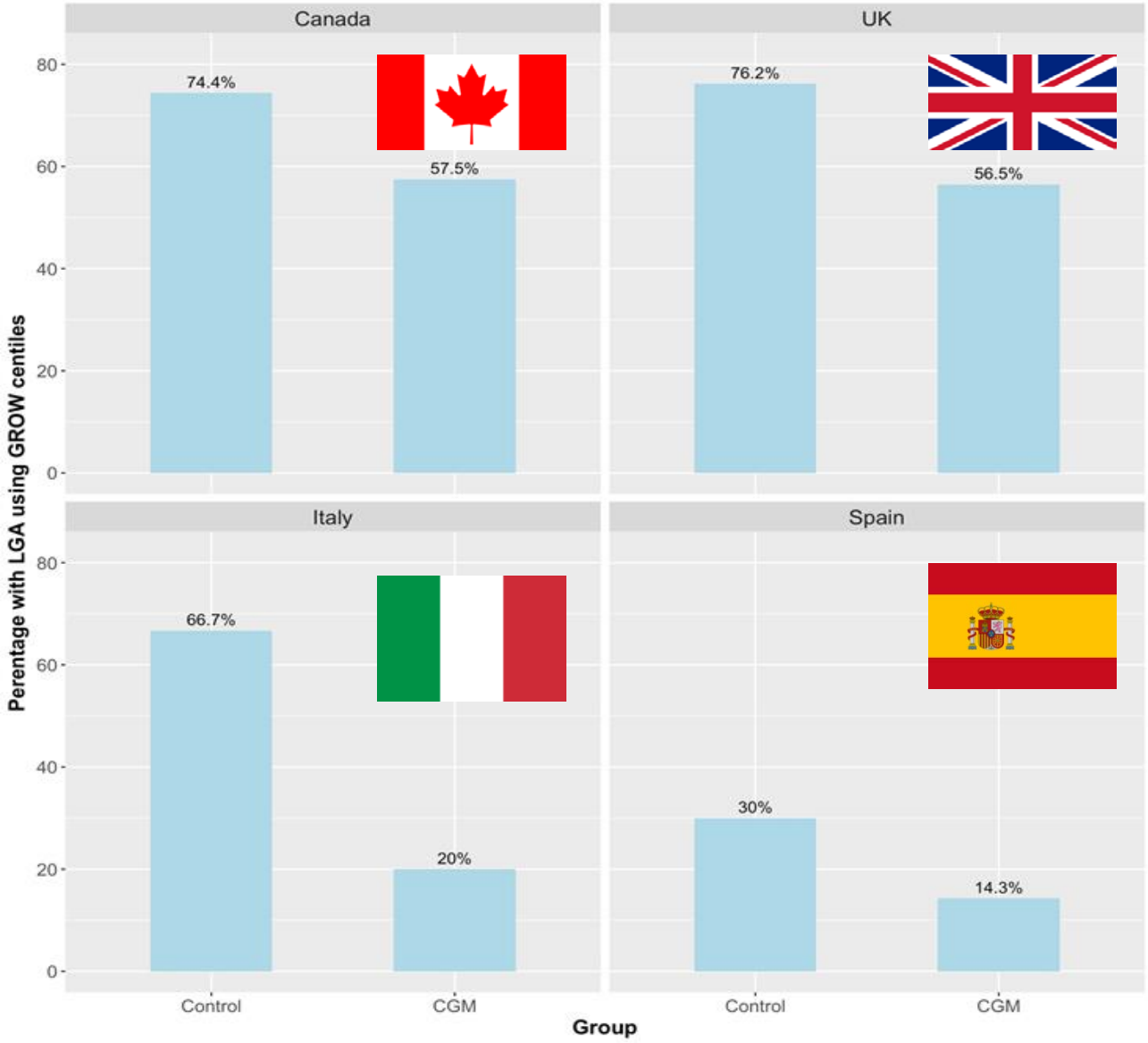
◊ In base ad etnia materna, altezza, peso, sesso del neonato ed epoca gestazionale al parto

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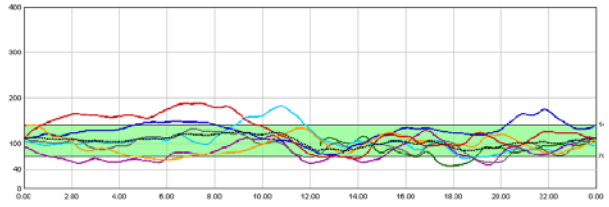
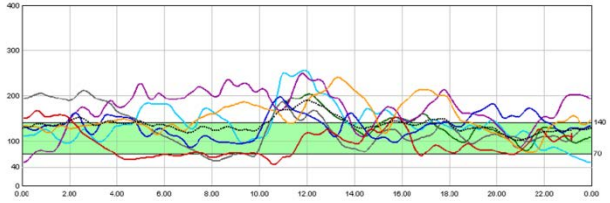
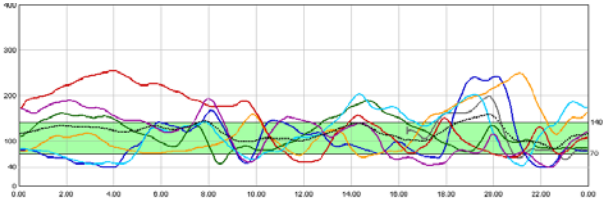
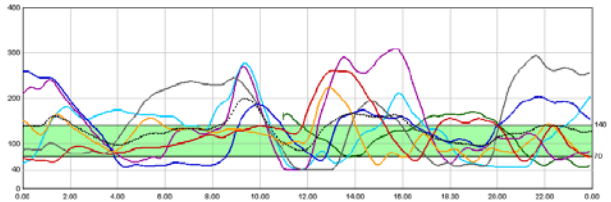
# CENTILE DI PESO ALLA NASCITA PER NAZIONE

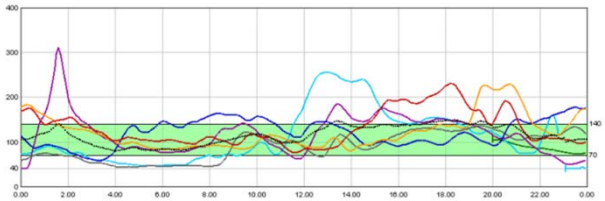
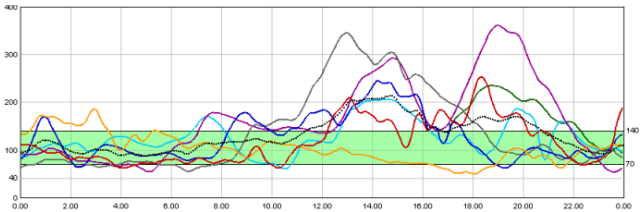
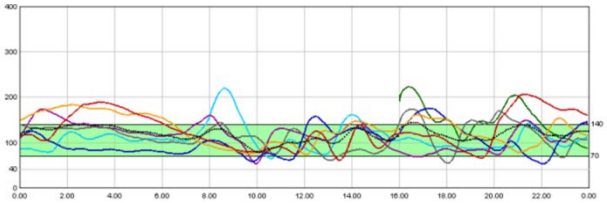
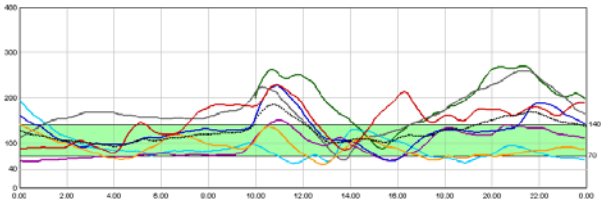
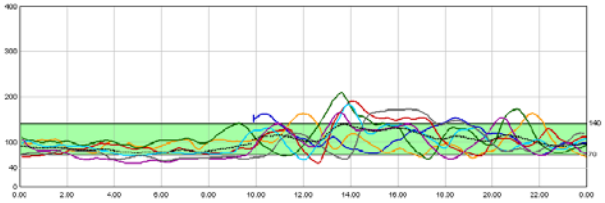
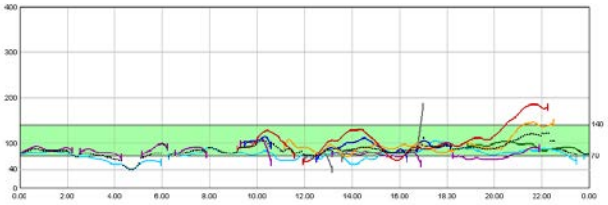
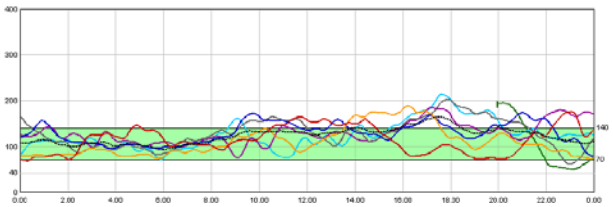


# FREQUENZA DI LGA PER NAZIONE



# MONITORAGGI ALLA 34 a SETTIMANA

# ALTRI ESITI NEONATALI

| | CGM | Controlli | P-value |
|---|---|---|---|
| | N=100 | N=100 | |
| Trauma da parto | 1 | 0 | 1.0 |
| Distocia di spalla | 1 | 0 | 1.0 |
| **Ipoglicemia neonatale** | **15.0%** | **28.0%** | **0.025** |
| Ipebilirubinemia | 25.0% | 31.0% | 0.43 |
| Distress respiratorio | 9.0% | 9.0% | 1.0 |
| **Degenza in NICU >24 hours** | **27.0%** | **43.0%** | **0.016** |
| Outcome neonatale composito[1] | 42.9% | 52.8% | 0.17 |

[1] **Comprende**: Perdita della gravidanza (aborto, MEF, morte neonatale) - Trauma da parto – Ipoglicemia neonatale – Iperbilirubinemia – Distress respiratorio – NICU >24 h.

CONCEPTT

# CONCEPTT Summary

- Pregnant women using CGM had lower HbA1c and better day-to-day glucose levels (100 mins/day)
- GCM effects were comparable among insulin pump and MDI users and across 31 international sites
- We found no consistent benefit of CGM in women planning pregnancy
- Babies of mothers using CGM had reduced risk of
  Large for gestational age, NICU admissions > 24 hours, Neonatal hypoglycaemia requiring iv dextrose, 1 day shorter hospital stay
- The NNT were very low (6-8) with potential for cost savings

# CONCEPTT - CONCLUSION

- **Use of CGM in Type 1 Diabetes pregnancy is associated with improved neonatal outcomes, attributed to reduced exposure to maternal hyperglycemia**
- **This is the first trial to demonstrate benefit of CGM on health outcomes beyond glucose control**
- **CGM should be offered to all pregnant women with Type 1 Diabetes using intensive insulin therapy**

# LA PUBBLICAZIONE




## Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial

*Denice S Feig, Lois E Donovan, Rosa Corcoy, Kellie E Murphy, Stephanie A Amiel, Katharine F Hunt, Elisabeth Asztalos, Jon FR Barrett, J Johanna Sanchez, Alberto De Leiva, Moshe Hod, Lois Jovanovic, Erin Keely, Ruth McManus, Eileen K Hutton, Claire L Meek, Zoe A Stewart, Tim Wysocki, Robert O'Brien, Katrina Ruedy, Craig Kollman, George Tomlinson, and Helen R Murphy, on behalf of the CONCEPTT Collaborative Group**

### Summary

**Background** Pregnant women with type 1 diabetes are a high-risk population who are recommended to strive for optimal glucose control, but neonatal outcomes attributed to maternal hyperglycaemia remain suboptimal. Our aim was to examine the effectiveness of continuous glucose monitoring (CGM) on maternal glucose control and obstetric and neonatal health outcomes.

**Methods** In this multicentre, open-label, randomised controlled trial, we recruited women aged 18–40 years with type 1 diabetes for a minimum of 12 months who were receiving intensive insulin therapy. Participants were pregnant (≤13 weeks and 6 days' gestation) or planning pregnancy from 31 hospitals in Canada, England, Scotland, Spain, Italy, Ireland, and the USA. We ran two trials in parallel for pregnant participants and for participants planning pregnancy. In both trials, participants were randomly assigned to either CGM in addition to capillary glucose monitoring or

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# COMMENTO E NUOVE PROSPETTIVE




Invited Review

**Continuous glucose monitoring in pregnant women with Type 1 diabetes: benefits for mothers, using pumps or pens, and their babies**

Diabet. Med. 35, 430–435 (2018)

D. S. Feig[1,2,3] and H. R. Murphy[4,5,6]

**Sensor-integrated or automated insulin delivery is definitely an exciting frontier for Type 1 diabetes pregnancy, but in the meantime women using injections or pumps with CGM can achieve close to 70% time-in-target-range.**

**Faster-acting insulins, newer-generation CGM devices and/or closed-loop systems might be needed to prevent postprandial highs which may help reduce neonatal adverse outcomes even further.**

# QUALCHE CONSIDERAZIONE AGGIUNTIVA

- **Risultati dello studio sulle donne in programmazione da considerare criticamente**
  - **Minore numerosità**
  - **Forse minore motivazione**
  - **Entità della differenza nel controllo glicemico in realtà simile allo studio sulle gravide**
- **Eterogeneità dei centri coinvolti, (da 14 a 31, per iniziale difficoltà di arruolamento), molti con casistica minima.**
- **Possibile influenza sugli esiti del gruppo CGM, a maggiore complessità di gestione**


Grazie!