

Clinical Controversies: Metformin in Pregnancy



Dr Helen Murphy
West Midlands Perinatal Forum
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French lilac – *galega officinalis*



Mechanism of action



- ↓ hepatic gluconeogenesis ~ 30%
- ↓ free fatty acid levels
- ↑ peripheral glucose uptake
i.e. ↑ insulin sensitivity

- Stimulates hepatic AMPK
- Molecular targets ??
- Excreted in urine – T_{1/2} ~ 6.2 hours

Pharmacokinetics



- Oral availability (50-60%) inversely related to dose
- Eliminated almost unchanged in urine – negligible plasma protein binding – renal clearance > GFR
- Absorption influenced by
 - food (↓ absorption ~ 20%)
 - GI transit time (↓ motility ~ 20%)
- During pregnancy: ↓gut motility and ↑GFR 40-50% i.e. max renal clearance as insulin resistance increases
 - Peak serum concentrations during pregnancy 80% of post-partum values (R Hughes, Diabetic Medicine 2006)

Role of Metformin in PCOS



PCOS women
Anovulatory infertility
n = 626

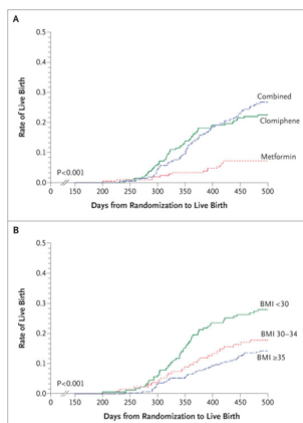
Clomiphene (CC)
n=209
Ovulation – 24.9%
Conception – 39.5%
LB – (47) 22.5%

Metformin SR
n=208
Ovulation – 44.7%
Conception – 21.7%
LB – (15) 7.2%

Combined CC+MF
n=209
Ovulation – 16.7%
Conception – 42%
LB – (56) 26.8%

Legro RS NEJM Feb 8th 2007

Live births



Clomiphene

- -↑Pregnancy rates x 2
- -↑Live births x 3
- -↑Multiple pregnancy – not monitored

Metformin

- stopped when pregnant
- benefits on pregnancy loss, PET and GDM??

Legro RS NEJM Feb 8th 2007

Preliminary MIG results



- No difference primary outcome composite
 - MF 32% vs Insulin 32.2% RR1.0 (0.9-1.0); p=0.95
 - No difference in hypoglycaemia <2.6mmol/L but ↓severe hypoglycaemia <1.6mmol/L in MF group
 - ↑ spontaneous preterm births in MF group; p=0.04 (mean gest age 38.3 vs 38.5 weeks; p=0.02)
- No difference in secondary outcomes
- 46% of MF group required insulin (BMI 36) and 20% had abnormal post partum GTT
- Insulin doses significantly lower in MF group

Personal Communication J Rowan Jan 2008
Manuscript In Press

South African retrospective Women with T2DM 1991-2000



	OGLA alone* n=93	OGLA to insulin n=249	Diet-Insulin n=37	P-values
Age	34.5±0.5	33.4±0.3	31.4±0.9	0.0006
Booking gestation	21.6±0.9	18.1±0.5	13.4±1.4	<0.001
Perinatal mortality	11/88 125/1000	7/248 28/1000	1/30 33/1000	0.003
Stillbirth	8/88 91/1000	5/248 20/1000	1/30 33/1000	0.01
Congen Anomaly	5/88 125/1000	5/248 20/1000	0/30 0/1000	NS
Macrosomia >4kg	23%	18%	17%	NS

*24/93 (25%) OGLA women major adverse event

Authors conclude that OGLA **not** associated with congenital anomaly but **is** independently associated with perinatal mortality

C.O. Ekpebegh et al 2007

East Anglia pregnancy complication and outcome data



	T1DM (n=389)	T2DM (n=146)	p value
Birth weight			
SGA < 10 th centile	3.6%	9.6%	<0.02
LGA > 90 th centile	46.5%	46.9%	NS
Congenital malform	17 (4.4%)	18 (12.3%)	<0.02
Perinatal mortality	11 (2.8%)	9 (6.2%)	NS
Serious adverse outcome	25 (6.4%)	24 (16.4%)	0.002

Roland JM Diabetic Med 2005

East Anglia risk of congenital malformation in T2DM



Independent Association	Odds Ratio (95% CI)	P
Oral Hypoglycaemic Agents*	1.8 (1.0-3.3)	0.04
BMI	1.09 (1.01-.18)	0.02
Folic Acid at Conception	0.3 (0.09-1.0)	0.04

* 45% women were taking OHA i.e. metformin, sulphonylurea or both

Influence of prepregnancy care (PPC)
in T1DM (n=290)



HbA1c %	PPC*	No PPC	P value
Booking	6.5	7.6	0.0001
12/40	5.9	6.6	0.0001
16/40	5.7	6.1	0.002
20/40	5.5	5.8	0.01
24/40	5.5	5.7	0.045
28/40	5.5	5.8	NS
32/40	5.6	5.8	NS

- ↓ malformation, stillbirth and neonatal death
- ↓ premature delivery <34/40

Diab Care & BJOG 2006

• **No difference in risk of macrosomia**

CGMS profiles in obese and normal
weight non-diabetic pregnant women



Normal weight (n=42)

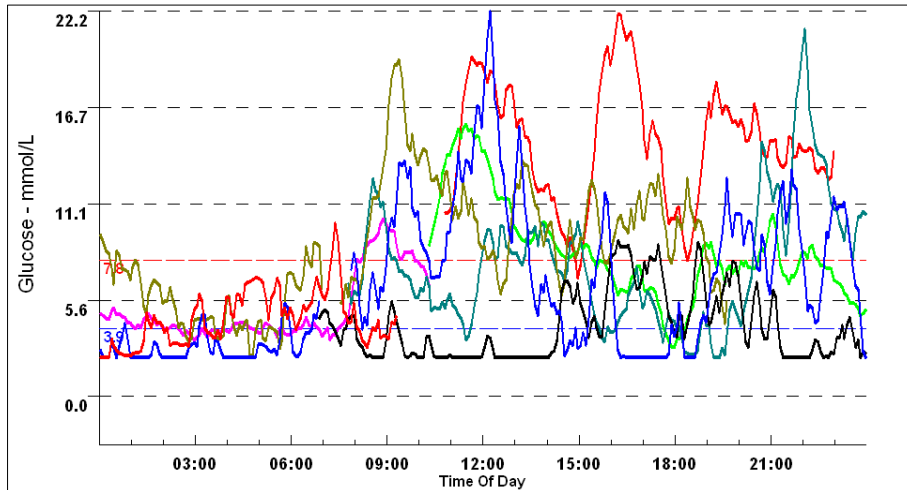
- FBG: 4.4 +/- 0.7 mmol/L
- Mean BG: 4.9 +/- 1.0 mmol/L
- PP peak BG: at 70 +/- 13 minutes: 6.5 +/- 0.9 mmol/L
- Overnight MBG: 4.0 mmol/L

Obese (n=15)

- Same FBG & MBG
- ↑ peak postprandial glucose 9.5 mmol/L
- ↑ 1-hr, 2-hr and 3-hr glucose
- ↑ time to PP peak 88 +/- 31 mins
- Lower overnight MBG 3.3 mmol/L

Yogev AMJOG 2004

CGMS Case Study- type 2 DM Booking visit 8/40 (HbA1c 6.6%)



Role of Metformin in T2DM? Big vs Small babies



Metformin probably safe
in pregnancy

- No benefit in PCOS
- Useful in ~25% GDM
- Will it help improve neonatal outcomes for infants of women with T2DM?