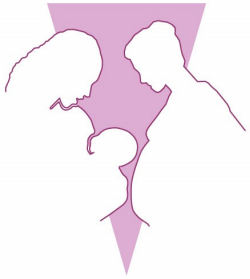


Design Considerations for Pharmacokinetic Studies during Pregnancy

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Conflicts of Interest

- None

Disclosure of Unlabeled/Unapproved Uses

- Glyburide and metformin are not FDA approved for management of gestational diabetes mellitus.
 - Glyburide: adjunct to diet and exercise for adults with type 2 diabetes mellitus (T2DM)
 - Metformin: adjunct to diet and exercise for adults and children with T2DM
- Alternate dosage strategies for glyburide, metformin and oseltamivir during pregnancy are not FDA approved.
 - FDA approved dosage:
 - Glyburide: 1.25-20 mg/day in single or divided doses
 - Metformin: 850-2550 mg/day in single or divided doses
 - Oseltamivir
 - Treatment dose: 75 mg twice daily for 5 days and
 - Prophylaxis: 75 mg once daily for at least 10 days (Community outbreak: 75 mg once daily for up to 6 weeks)

Dedicated Pharmacokinetic Studies

Advantages

- Feasibility
 - Limit expectation of subjects that are receiving the drug for therapeutic reasons
- Risks
 - Generally minimal if blood volume needs are low and patient already receiving the drug
- Recruitment
 - Fairly easy if patient is already receiving the drug

Disadvantages

- Feasibility
 - Requires giving the drug if patients are not already receiving it (new drugs, older drugs of interest if patient not already receiving the drug)
- Minimal risk requirements

Nested Studies

Advantages

- Efficiency
 - Gather efficacy and safety data at the same time as pharmacokinetic data
- Recruitment
 - If the population that needs the drug is small, might be the only way to collect the data
- Risks
 - Patients will be receiving the drug anyway for therapeutic reasons

Disadvantages

- Feasibility
 - The more that pregnant women are asked to do, the harder it is to recruit...particularly if they also have small children

Dose Selection

- Opportunistic study
 - Currently used dosage for therapeutic reasons
- Not opportunistic studies
 - Consider the consequences of under- and over-dosing

Oseltamivir

- Influenza/H1N1 in pregnancy
 - Morbidity and mortality higher in pregnant women
- Wide margin of safety
- PK
 - Oseltamivir
 - Well absorbed
 - Rapidly converted to the active metabolite oseltamivir carboxylate by carboxylesterase-1
 - Less than 5% excreted in the urine unchanged.
 - Oseltamivir carboxylate
 - Primary route of elimination: kidney
 - Filtered
 - Secreted by OAT1

Package insert. Am J Obstet Gynecol. 2011;204(6 Suppl 1):S84-8.

MMWR Morb Mortal Wkly Rep 2008;57(RR-7):1-60. JAMA 1918; 71:1898-9.

Am J Ob- stet Gynecol 1958;76:897-902. Obstet Gynecol 2007;109:1193-6.

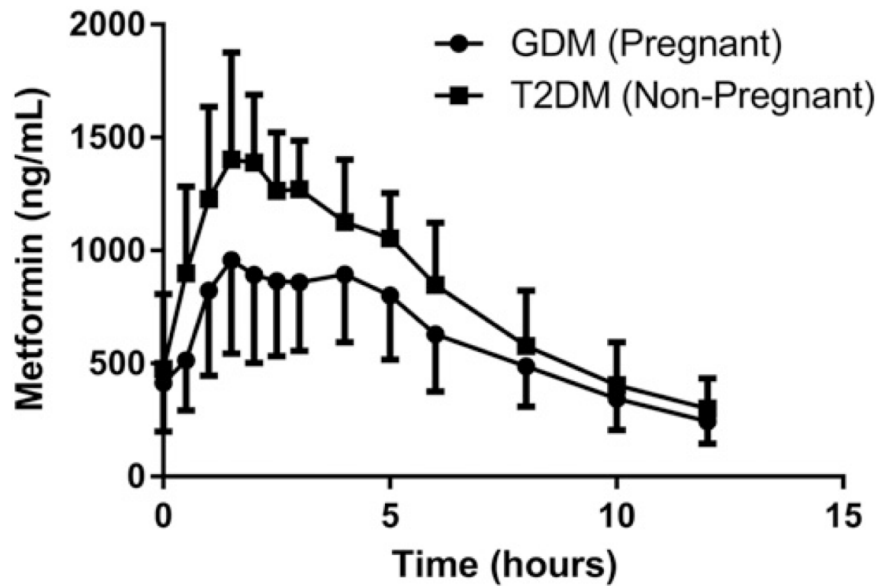
Lancet 2009;374:451-8. N Engl J Med 2010;362:27-35. Clin Infect Dis 2010;50:686-90.

Oseltamivir in Pregnancy (n=16 pregnant women and n=23 non-pregnant female controls)

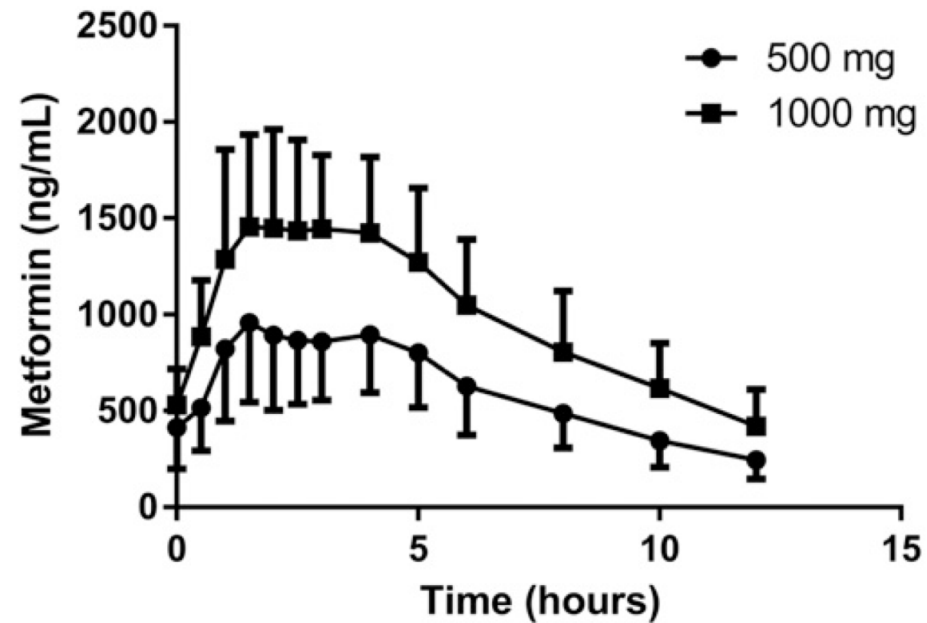
- No change in oseltamivir CL/F
- 44% increase in oseltamivir carboxylate CL/F ($p = 0.006$)

Metformin starting dosage?

Pregnant vs. Non-pregnant 500 mg bid



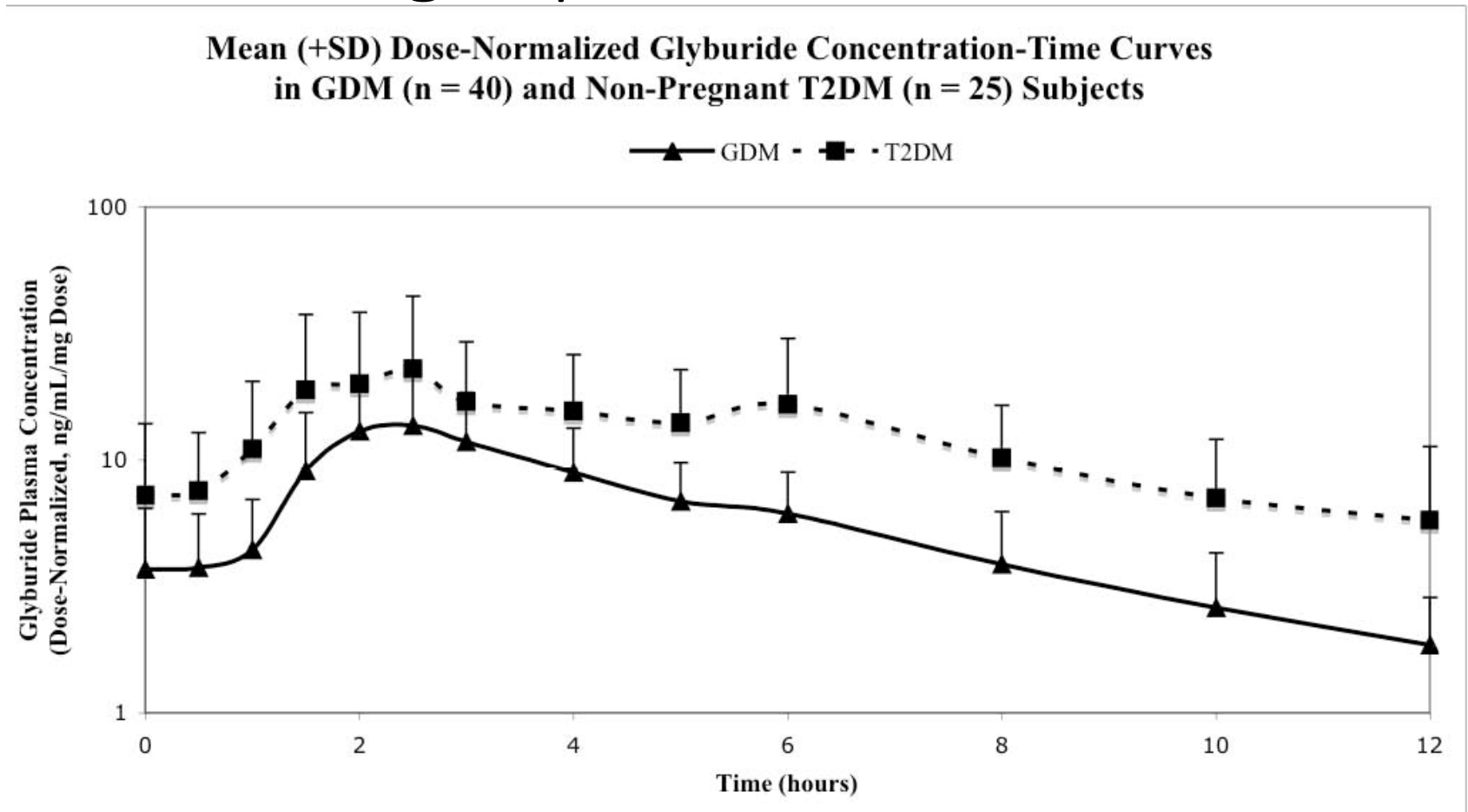
Metformin in Pregnancy



Metformin PK in GDM vs T2DM

	500 mg Pregnant (n = 39)	500 mg Nonpregnant (n = 9)	P Value	1000 mg Pregnant (n = 15)	1000 mg Nonpregnant (n = 14)	P Value
Metformin						
F	0.64 ± 0.2	0.49 ± 0.08	<0.01	0.53 ± 0.11	0.37 ± 0.14	<0.01
Half-life (h)	4.2 ± 1.1	4.0 ± 0.8	0.4	4.3 ± 0.7	3.7 ± 0.6	0.2
Tmax (h)	2.6 ± 1.3	2.1 ± 0.5	<0.01	2.4 ± 1.1	2.2 ± 1.3	0.7
V _B /F (l)	368 ± 133	276 ± 52	<0.05	450 ± 136	486 ± 207	0.6
V _B /F (l/kg)	4.00 ± 1.68	3.19 ± 1.10	0.08	4.99 ± 1.64	5.00 ± 2.07	0.9
V _B (l)	242 ± 138	134 ± 23	<0.001	234 ± 66	163 ± 48	<0.005
V _R (l/kg)	2.6 ± 1.6	1.5 ± 0.3	<0.005	2.6 ± 0.9	1.7 ± 0.6	<0.005
CL/F (ml/min)	1085 ± 328	854 ± 230	<0.05	1405 ± 384	1678 ± 574	0.4
CL/F (ml/min per kilogram)	11.7 ± 3.8	9.5 ± 2.4	0.05	15.6 ± 4.5	17.5 ± 6.5	0.3
CL (ml/min)	731 ± 339	444 ± 121	<0.01	758 ± 179	572 ± 153	<0.05
CL (ml/min per kilogram)	7.9 ± 3.9	4.9 ± 1.3	<0.01	8.5 ± 2.5	6.1 ± 2.4	<0.05
Percent of dose recovered in the urine unchanged (%)	64 ± 20	49 ± 8	<0.01	53 ± 11	37 ± 14	<0.01
CL _R (ml/min)	731 ± 339	444 ± 121	<0.01	758 ± 179	572 ± 153	<0.05
CL _R (ml/min per kilogram)	7.9 ± 3.9	4.9 ± 1.3	<0.01	8.5 ± 2.5	6.1 ± 2.4	<0.05
CrCL (ml/min)	233 ± 68	148 ± 41	<0.001	233 ± 46	166 ± 25	<0.001
CL _{sec} (ml/min)	497 ± 312	296 ± 97	0.06	530 ± 168	406 ± 143	0.1
CL _{sec} (ml/min per kilogram)	5.4 ± 3.6	3.3 ± 1.1	<0.05	5.9 ± 2.3	4.3 ± 2.0	0.2

Glyburide Drug Exposure in GDM vs. T2DM

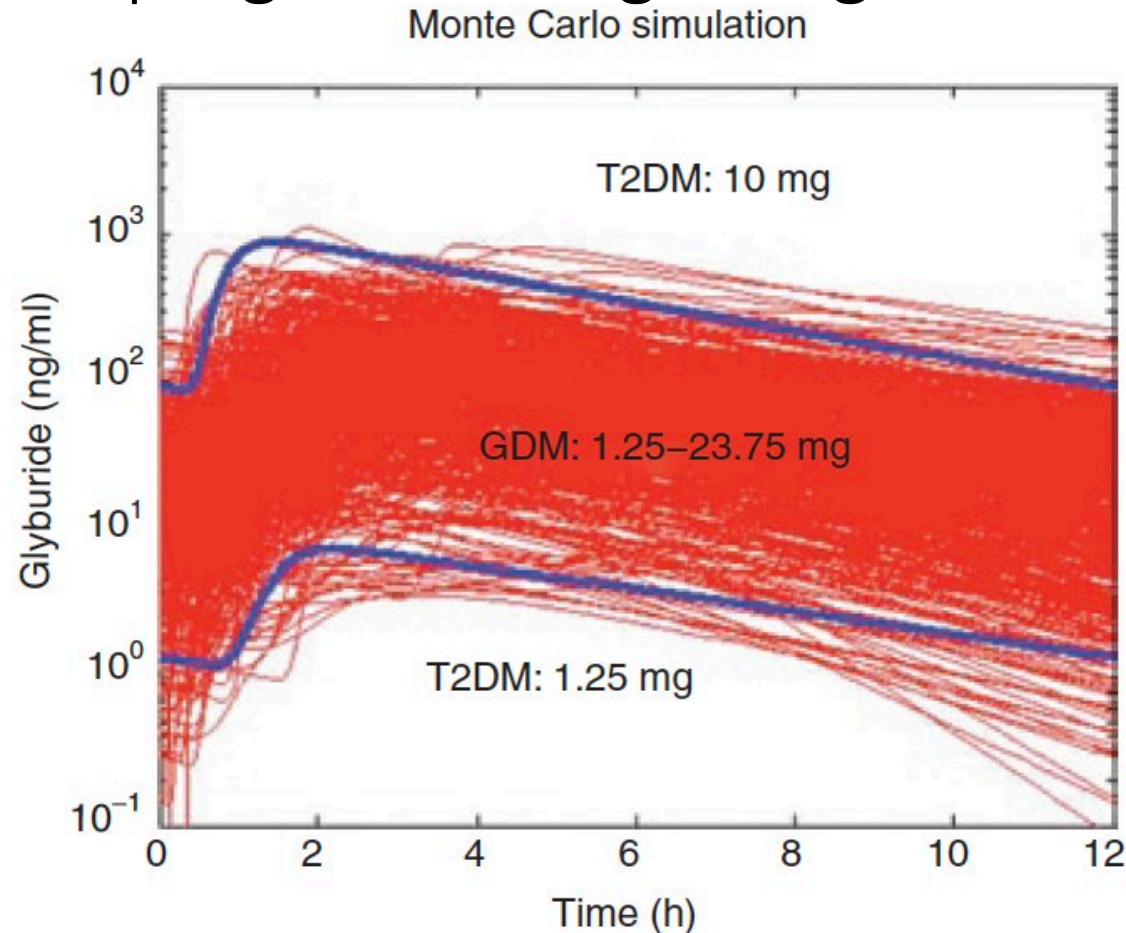


Dose-normalized, steady-state, mean glyburide plasma concentration–time profiles in subjects with gestational diabetes mellitus (GDM) (n = 40) and in nonpregnant control subjects with type 2 diabetes mellitus (T2DM) (n = 25). Error bars represent SDs.

Glyburide PK in GDM vs T2DM

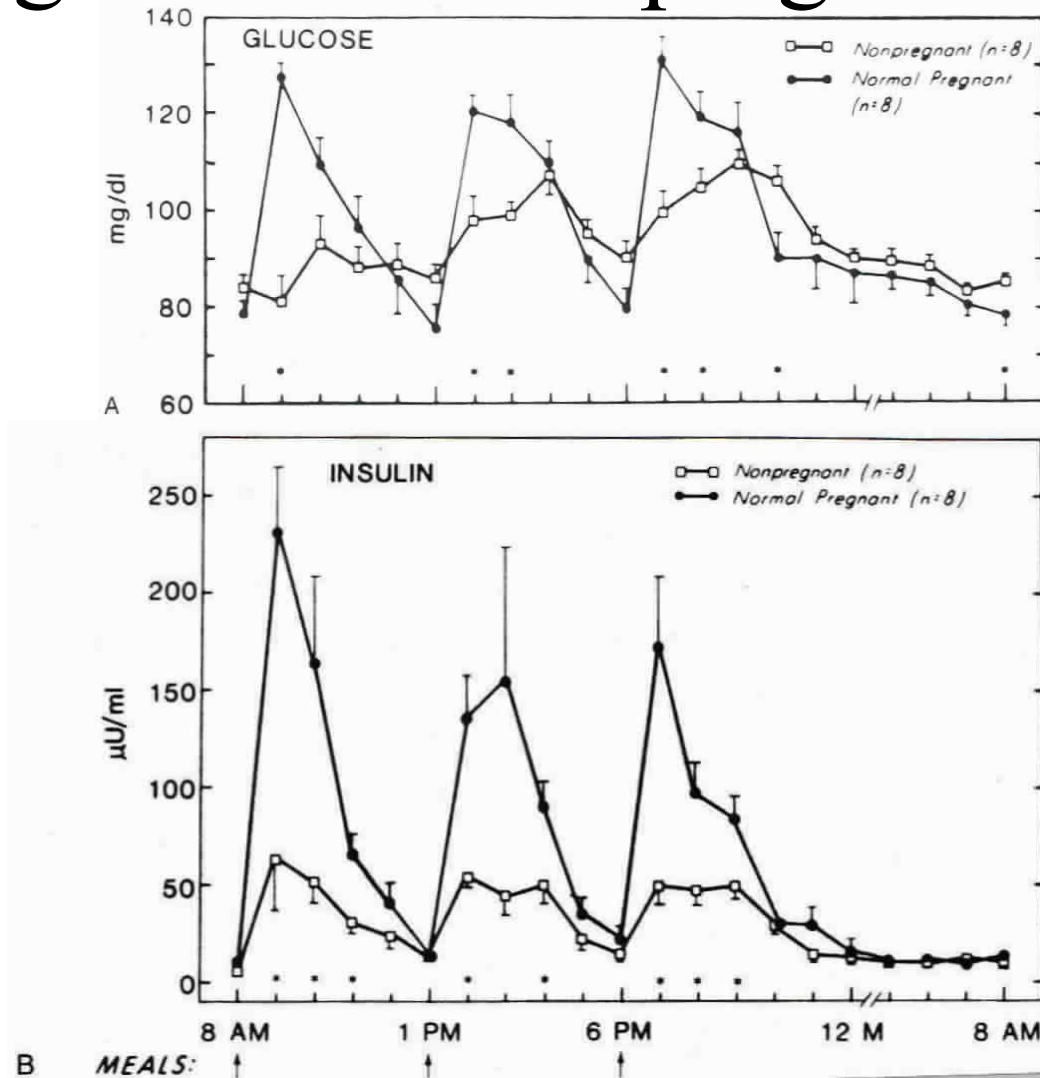
Parameters	GDM	T2DM	Percent change in mean with pregnancy (%)	P value
$AUC_{0 \rightarrow 12, \text{dose normalized}}$ (ng·h/ml)	72 ± 27	153 ± 69^a	↓53	0.0001
$C_{\text{max, dose normalized}}$ (ng/ml)	15 ± 8	33 ± 21^a	↓55	<0.0001
CL/F (l/h)	17.1 ± 11.5	8.3 ± 4.8	↑106	<0.0001
CL/F (ml/h/kg)	170 ± 88	85 ± 53	↑100	<0.0001
CL/F _{unbound} (l/h)	$1,103 \pm 749$	537 ± 313	↑105	<0.0001
CL/F _{unbound} (l/h/kg)	10.9 ± 5.8	5.5 ± 3.4	↑98	<0.0001
Percent unbound (%)	1.6 ± 0.1	1.5 ± 0.1	↔	0.2
T_{max} (h)	3.0 ± 1.5	3.5 ± 1.9	↔	0.4
CL _{form, 4-trans-OH-gly} (l/h)	4.7 ± 2.6	2.0 ± 0.9	↑135	<0.0001
CL _{form, 4-trans-OH-gly} (ml/h/kg)	48.9 ± 28.7	20.1 ± 8.6	↑143	<0.0001
CL _{unbound form, 4-trans-OH-gly} (l/h)	303 ± 184	128 ± 59	↑137	<0.0001
CL _{unbound form, 4-trans-OH-gly} (l/h/kg)	3.2 ± 2.0	1.3 ± 0.6	↑146	<0.0001
$AUC_{4\text{-trans-OH-gly}}/AUC_{\text{gly}}$	0.26 ± 0.22	0.14 ± 0.12	↑89	0.005

How much glyburide do you need to give in pregnancy to match non-pregnant dosage range?



Semilogarithmic plot of simulated steady-state glyburide plasma concentration–time curves in subjects with gestational diabetes, denoted by red lines (1.25–23.75 mg glyburide every 12 h) and nonpregnant control subjects with type 2 diabetes (1.25–10 mg of glyburide every 12 h) with the 99% confidence interval bordered by blue lines. The simulations are based on 100 sets of parameters at each dosage, with dosage being increased in increments of 1.25 mg within the dosage range for both groups. GDM, gestational diabetes mellitus; T2DM, type 2 diabetes mellitus.

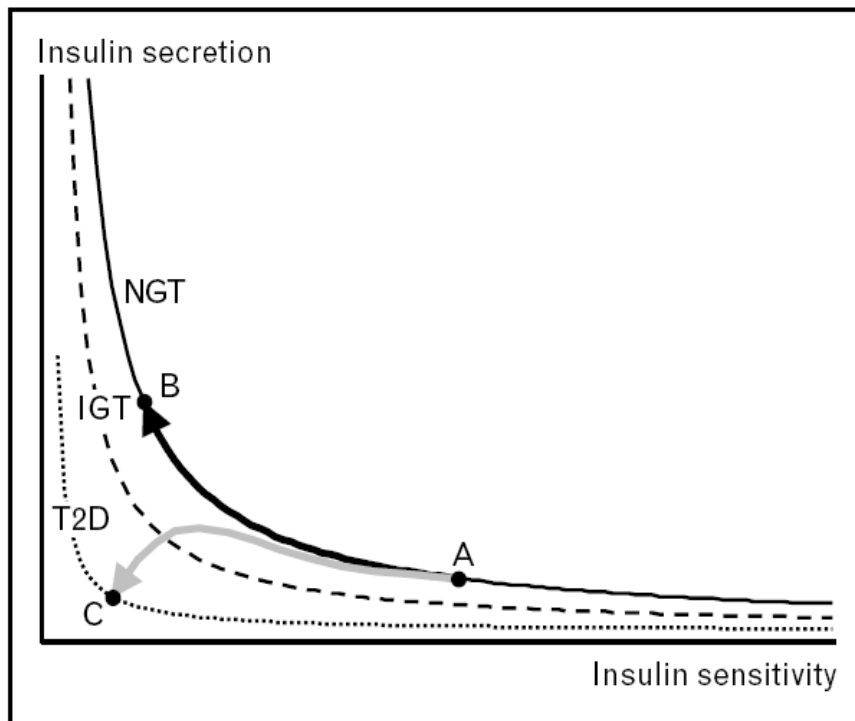
Glucose and Insulin Concentrations in Pregnant and Nonpregnant Subjects



Phelps et al. Am J Obstet Gynecol 1981;140:730.

Hyperbolic relationship

$$\text{Insulin Secretion} \times \text{Insulin Action} = \text{Disposition Index (Constant)}$$



Insulin sensitivity ↓

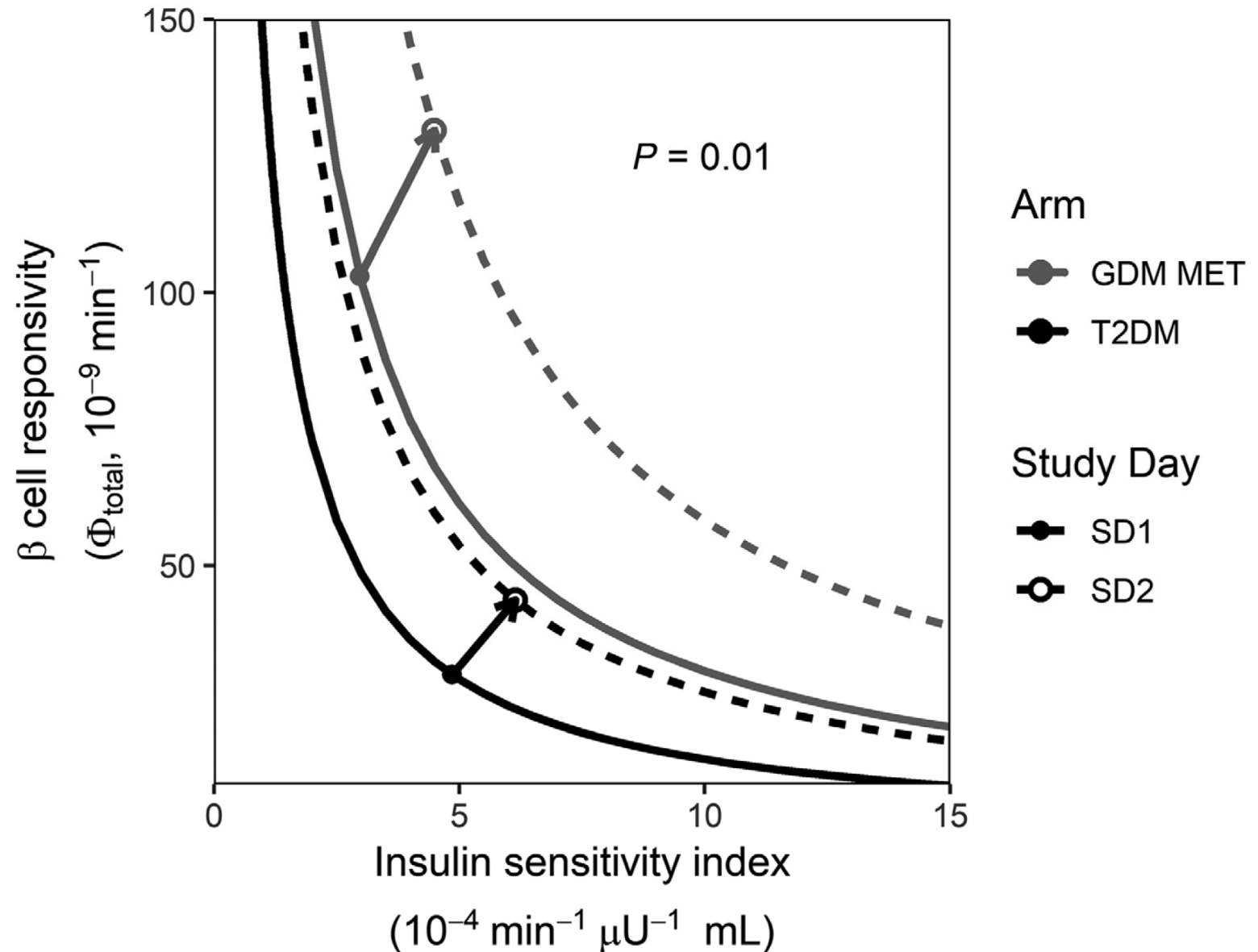
Compensated by Beta-cell function ↑

Disposition Index (DI):

❖ An index of beta-cell secretion that accounts for insulin sensitivity.

❖ Ability of the pancreatic beta-cells to compensate for insulin resistance by increasing beta-cell responsiveness.

Metformin PD GDM vs. T2DM



Effects of GLY, MET and GLY/MET Combo in GDM

