

Don't Sugar Coat It: Best Practices for Diabetes Management in Pregnancy

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UAB MATERNAL-FETAL MEDICINE

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OBJECTIVES



Describe the impact of diabetes in terms of disease prevalence, cost, and maternal & perinatal complications.



Discuss the current evidence regarding GDM screening, diagnosis and treatment.



Understand the importance of and barriers to postpartum diabetes screening after GDM.



Identify knowledge gaps surrounding use of oral hypoglycemic agents for pregestational diabetes.



Review new technologies surrounding the treatment of diabetes in pregnancy.







3.7 MILLION deaths due to diabetes and high blood glucose

1.5 MILLION deaths caused by diabetes



Burden of Disease

THAT'S 1 PERSON IN 11



IDF DIABETES ATLAS

9th edition 2019

under the age of 60



GLOBAL Fact sheet

Number of adults (20–79 years) with diabetes worldwide



in people under the age of 60

WORLD

🚥 700 million 🛧 51% 578 million 463 million

increase

Europe

68 million 15% no//im 66 million increase 59 million

 1 in 8 live births are affected by hyperglycaemia in pregnancy The Region has the highest. number of children and adologamta (0-19 yours) with type i diabetes - 297,000 in total

Western Pacific

🚥 212 million 🚲 31% 197 million 💷 163 million

- I in 8 adults with diabetes lives in this Region

occur in this Region

Lin 4 live births are attracted by

hyperglyceemia in pregnancy

increase

Lin 3 deaths due to diabetes.

Where Diabetes is Most Prevalent in the U.S.

Percent of adults who have ever been told by a doctor that they have diabetes (2017*)







Learn how to combat this costly disease at **diabetes.org/congress**





1 in **6** live births occur to women with some form of hyperglycemia

84% of which are due to GDM

HYPERGLYCEMIA/GDM IS ASSOCIATED WITH:

- Leading causes of maternal mortality
- Higher incidence of maternal morbidity
- Higher incidence of perinatal and neonatal morbidity
- · Later long term consequences for both mother and child



Low and middle income countries account for:

- 85% of the annual global deliveries
- 80% of the global diabetes burden
- 90% of all cases of maternal and perinatal deaths and poor pregnancy outcomes

PREGNANCY OFFERS A WINDOW OF OPPORTUNITY TO:

- Establish services
- → Improve health
- Prevent intergenerational transmission of noncommunicable diseases

Complications of Diabetes

MATERNAL:

Hypertension or preeclampsia

Worsening comorbid conditions (retinopathy)

Preterm birth

Cesarean delivery

Future risk for T2DM

NEONATAL:

Congenital malformations

Stillbirth

LGA or SGA

Shoulder dystocia & birth injury

Respiratory problems

NICU admission

Future risk of chronic disease

GDM SCREENING, DIAGNOSIS, AND TREATMENT

Historical Context

In 1960s, screening for GDM was aimed at identifying women who would develop T2DM later in life

In 2000s, demonstrated that the increased maternal and fetal risks associated with GDM could be mitigated with treatment during pregnancy



Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes

Caroline A. Crowther, F.R.A.N.Z.C.O.G., Janet E. Hiller, Ph.D., John R. Moss, F.C.H.S.E., Andrew J. McPhee, F.R.A.C.P., William S. Jeffries, F.R.A.C.P., and Jeffrey S. Robinson, F.R.A.N.Z.C.O.G., for the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group*

 Randomized clinical trial to determine whether treatment of women with GDM reduced the risk of perinatal complications

\square N=1000 women

Intervention (nutrition consult, self-glucose monitoring 4x/day, insulin)

Image: Routine care

Table 2. Primary Clinical Outcomes among the Infants and Their Mothers.*							
Outcome	Intervention Group	Routine- Care Group	Unadjusted Relative Risk (95% CI)	Unadjusted P Value	Adjusted Relative Risk (95% Cl)†	Adjusted P Value†	Step-Down Sidak P Value
	no.	(%)					
Infants							
Total no.	506	524					
Any serious perinatal complication;	7 (1)	23 (4)	0.32 (0.14-0.73)	0.004	0.33 (0.14-0.75)	0.01	0.04
Death	0	5 (1)		0.06		0.07	
Stillbirth	0	3 (1)§		0.25		0.26	
Neonatal death	0	2 (<1)		0.50		0.50	
Shoulder dystocia¶	7 (1)	16 (3)	0.45 (0.19–1.09)	0.07	0.46 (0.19–1.10)	0.08	
Bone fracture	0	1 (<1)		1.00		0.38	
Nerve palsy	0	3 (1)		0.25		0.11	

TREATMENT OF GDM DECREASES THE RISK OF SERIOUS PERINATAL COMPLICATION BY 70% (NNT = 34)

Recommend Universal Screening for GDM at 24-28 weeks' Gestation

Universal screening in US: up to 80% of women have at least one risk factor and **20% have <u>no</u> risk factors** (USPTF 2014)

> Meta-analysis of 29 studies (n>211,000 women) concluded that risk factors were **poor predictors** of women who had an abnormal GTT

Universal (versus selective) screening shown to be cost-effective in numerous countries

> Danilenko-Dixon Dr AM J Obstet Gynecol 1999;181:798

Farrar D *PLoS One* 2017;12:e0175288

One versus Two-step Screening



- Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study
- 25,505 pregnant people
- 15 centers in 9 countries
- 2hr, 75g GTT at 24-32wk
- Objective = identify outcomes-based cutoffs for GDM diagnosis



One versus Two-step Screening





 \Box One-step identifies more GDM (~18% vs ~6%) Patients identified as GDM on one-step who have normal two-step screening have "milder" disease, but may still be at risk for adverse pregnancy outcomes One-step screening may increase healthcare costs and patient anxiety without clear benefit in pregnancy □ Implications are unknown when long-term impact is considered

Treatment of GDM

Nutrition Assessment and Education

Exercise/Activity Counseling

Diabetes Education

Pharmacotherapy as needed
Insulin

Oral hypoglycemic agents



Goals for Treatment

Blood Glucose	ACOG	ADA
Fasting	<95	60-99
1 hr postprandial	<140	<140
2 hr postprandial	<120	<120





Pharmacologic Treatment Options

- 1. Insulin
- 2. Metformin* "first-line alternative to insulin"
- Glyburide* inferior to both insulin and metformin
- *Cross placenta with uncertain long-term effects





GDM Treatment and Neonatal Hypoglycemia

	Glibenc	lamide	Insu	ılin				
Study or subgroup	No of events	No of births	No of events	No of births		Risk ratio (95% CI)*	Weigl (%)	nt Risk ratio (95% CI)*
Glibenclamide v insulin								
Langer et al 2000 ²	18	201	12	203			47.4	1.51 (0.75 to 3.06)
Anjalakshi et al 2007 ²¹	0	9	0	13				
Ogunyemi et al 2007 ²²	12	43	6	45			23.3	2.09 (0.86 to 5.08)
Silva et al 2007 ²⁰	8	32	1	36			> 3.7	9.00 (1.19 to 68.09)
Lain et al 2009 ³	4	40	0	41			2.0	9.22 (0.51 to 165.87)
Mukhopadhyay et al 2012 ²³	4	30	3	30	-		11.9	1.33 (0.33 to 5.45)
Tempe et al 2013 ²⁴	4	31	3	32	-		11.7	1.38 (0.33 to 5.66)
Total	50	386	25	400			100.	2.04 (1.30 to 3.20)
Test for heterogeneity: $\chi^2=4.4$	5, df=5,	P=0.49, I	² =0%	0.0	0.1	1 10	50	

Favours glibenclamide

Test for overall effect: z=3.11, P=0.002

Metformine v glibenclamide Moore et al 2010³⁰

Silva et al 2012⁵

Total

Metformin v insulin	Metfe	Metformin		Insulin	
Moore et al 2007 ²⁵	0	31	2	3	
Rowan et al 2008 ⁴	55	363	69	3	
ljas et al 2011 ²⁶	4	47	7	3	
Niromanesh et al 2012 ²⁷	3	80	2	1	
Spaulonci et al 2013 ²⁹	3	46	10	2	
Tertti et al 2013 ²⁸	18	109	18	1	
Total	83	676	108	6	
Test for heterogeneity: $\chi^2=4$.	51, df=5,	P=0.48,1	² =0%		
Test for overall effect: z=1.87	, P=0.06				

Metformin

75

103

178

0

13

13

1

11

12

Test for heterogeneity: χ^2 =0.64, df=1, P=0.42, I²=0%

Test for overall effect: z=0.41, P=0.68

				100.0	0.78 (0.60 to 1.01
_		-	 -	16.9	0.98 (0.54 to 1.78
-				9.3	0.30 (0.09 to 1.02
-				1.9	1.50 (0.26 to 8.74
-	-		 	6.3	0.61 (0.19 to 1.94
-				63.4	0.81 (0.59 to 1.12
-		-		2.3	0.20 (0.01 to 4.00



Favours insulin



Early GDM Screening?

Risk-factor based

Uncertain gestational age range

Optimal screening test unknown

Vague guidelines not based on high-quality evidence

Box 1. Screening Strategy for Detecting Pregestational Diabetes or Early Gestational Diabetes Mellitus (=

Consider testing in all women who are overweight or obese (ie, have a body mass index greater than 25 or greater than 23 in Asian Americans) and have one or more of the following additional risk factors:

- Physical inactivity
- · First-degree relative with diabetes
- High-risk race or ethnicity (eg, African American, Latino, Native American, Asian American, Pacific Islander)
- Have previously given birth to an infant weighing 4,000g (approximately 9 lb) or more
- Previous gestational diabetes mellitus
- Hypertension (140/90 mm Hg or on therapy for hypertension)
- High-density lipoprotein cholesterol level less than 35 mg/dL (0.90 mmol/L), a triglyceride level greater than 250 mg/dL (2.82 mmol/L)
- Women with polycystic ovarian syndrome
- A_{1c} greater than or equal to 5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
- Other clinical conditions associated with insulin resistance (eg, prepregnancy body mass index greater than 40 kg/m², acanthosis nigricans)
- History of cardiovascular disease



<u>Primary outcome</u> = macrosomia, primary cesarean, hypertensive disease of pregnancy, shoulder dystocia, neonatal hyperbilirubinemia and hypoglycemia

Early GDM screening did not improve neonatal outcomes



Unanswered GDM Treatment Questions

When to initiate pharmacotherapy (1R01HD108194 – Palatnik)
Ideal glucose targets (1R01HD101476 – Scifres)
Best pharmacologic agent (R01 pending – Landon/Venkatesh)
Optimal timing of delivery (SPAN TIME)

CARE AFTER GDM



OUR RIGHT TO A HEALTHY FUTURE

Postpartu m Care

Nutrition counseling, exercise and lifestyle changes

2hr, 75g OGTT at 4-12wk postpartum*

Lifelong diabetes screening

- Every <u>3 years</u> if postpartum OGTT normal
- Every <u>**1 year**</u> if impaired glucose metabolism

Summary of results per 100,000 women

	No screening	2-step screening	1-step screening			
GDM diagnosed	0	5,020	17,800			
Future T2DM prevented	0	446	1,134			
Shoulder dystocia	1,051	995	910			
Preeclampsia	5,292	5,074	4,812			
Total QALY	5,563,323	5,565,646	5,571,824			
Total cost (2011 \$)	\$831 million	\$870 million	\$ 996 million			
Marginal cost/QALY*		16,689	20,336			
If NO long-term benefit (i.e. NO prevention of future T2DM):						
Total QALY	5,563,323	5,563,340	5,563,367			
Total cost (2011 \$)	\$831 million	\$840 million	\$ 856 million			
Marginal cost/QALY*		543,119	565,407			

*Each strategy compared to previous strategy (column to the left)

GDM screening is only cost-effective if provides long-term maternal health benefit

"Cost-effective" if incremental cost per quality adjusted life year **<\$100,000**



Bennett WL 2013; Blatt AJ 2011; Smirnakis KW 2005; Lawrence JM 2010; Hale NL 2012; Battarbee 2018

Barriers to Postpartum Diabetes Screening

Work/school

Childcare

Transportation

Insurance

Health attitude

Provider attention

GTT before hospital discharge?

Early Postpartum GTT: Feasibility

- 4 pilot studies comparing early (1-4 days post-partum) to routine post-partum GTTs
- All found early GTTs to be <u>feasible</u>
 1-4 day post-partum GTT adherence rate >90%
 4-12 week post-partum GTT adherence rate <50%

Early Postpartum GTT: Accuracy

Prospective cohort study of 300 patients with GDM comparing the diagnostic value of a 2-day postpartum GTT to the 4-12 week GTT in identifying impaired glucose metabolism and overt T2DM at 1 year postpartum.

296 (99%) completed 2-hr, 75-g GTT on PPD2
202 (67%) completed 2-hr, 75-g GTT at 4-12 weeks
203 (68%) completed HbA1c at 1 year

Glucose Results by Test Time

Impaired glucose metabolism Diabetes



Identifying Impaired Glucose Metabolism (A1c≥5.7%) at 1 year Postpartum

	2 day GTT	4-12 week GTT	1.00
Sensitivity	41% (29-53%)	28% (18-40%)	50 0.75
Specificity	78% (70-85%)	87% (80-92%)	Sensi
Positive Predictive Value	50% (37-63%)	54% (37-70%)	0.00 0.25 0.50 0.75 1.00 1-Specificity
	71% (63-78%)	69% (62-76%)	• 4-12 Weeks AUC: 0.58 (95% Cl: 0.52 - 0.64)

Identifying T2DM (A1c \geq 6.5%) at 1 year Postpartum

	2 day GTT	4-12 week GTT	
Sensitivity	67% (30-92%)	67% (3092%)	Sitivity 50 0.75
Specificity	73% (66-79%)	84% (78-89%)	Sen 0 0.25 0 0
Positive Predictive Value	10% (4-21%)	16% (6-32%)	0.00 0.25 0.50 0.75 1.00 1-Specificity
	98% (94-100%)	98% (95-100%)	Werner 2020

Early Postpartum GTT: Accuracy

2 day postpartum GTT is associated with 99% adherence

2 day postpartum GTT has a similar diagnostic value as the
4-12 week GTT in identifying impaired glucose metabolism at
1 year postpartum

Both the 2 day postpartum GTT and the 4-12 weeks GTT have high NPV for T2DM at 1 year postpartum

PREGESTATIONAL DIABETES IN PREGNANCY

Keys to Management of Pregestational Diabetes in Pregnancy

Preconception care to optimize diabetes and comorbidities

Achieve and maintain maternal euglycemiaDiet and exercisePharmacologic therapy

Surveillance of fetal growth and well-being





In∛окапа canagliflozin tablets pioglitazon HCI (exenatide) injection One

Insulin is the Preferred Treatment for T2DM in Pregnancy

"For those women with type 2 diabetes who decline insulin, those who their obstetricians or obstetric care providers believe will be unable to safely administer insulin, or those who cannot afford insulin, **metformin** (and rarely glyburide) is a *reasonable alternative choice* in the context of discussing with the patient the limitations of the <u>safety</u> data and a high rate of <u>treatment failure</u>, which requires insulin supplementation." –ACOG PB 201, December 2018 What about metformin for T2DM in pregnancy? First-line agent in non-pregnant adults with T2DM

Reduces glucose production in the liver, glucose absorption in the gut, and increases insulin receptor sensitivity

□3 RCTs, 241 women – no clear difference between metformin and insulin

I recent/ongoing RCTs
MiTy – Metformin in Women with T2DM in Pregnancy Trial (Feig, Canada; N=500)
MOMPOD – Medical Optimization of Management of T2DM Complicating Pregnancy (Boggess, U.S.; N=950)

Metformin in Type 2 Diabetes in Pregnancy: MiTy Trial

Prospective, international, double-masked RCT of metformin versus placebo added to insulin for treatment of T2DM in pregnancy (n=502)

Primary outcome was composite of:

- □ Pregnancy loss (miscarriage, termination, stillbirth, neonatal death)
- \Box Preterm birth < 37 weeks
- □ Birth injury
- □ Moderate or severe RDS
- □ Neonatal hypoglycemia
- □ NICU admission >24hr

Metformin in Type 2 Diabetes in Pregnancy: MiTy Trial



Better glycemic control

Less insulin

Gained less weight

Fewer cesarean deliveries

Smaller neonates at birth

No difference in hypertensive disorders or neonatal hypoglycemia

NEW DIABETES TECHNOLOGY

Continuous Glucose Monitor



Easily-administered subcutaneous glucose-sensing device

Image: Image:

Provide detailed data on glucose level, direction, and rate of change

Dexcom

G4, G5, G6 G4Pro, G6Pro



Medtronic Guardian, iPro2



Freestyle Libre, LibrePro

Senseonics Eversense



90-day Implantable Sensor subcutaneous

Removable Transmitter worn over skin



.)



Real-time or Retrospective No calibrations Link to t-slim pump Real-time or Retrospective Calibrations 2x/day Link to Medronic pump Intermittent or Retrospective No calibrations Less expensive, no alarms Real-time Calibrations 2x/day Implantable q 3mo

Available CGM Devices

Using CGM

Week 1









ADA Recommended Clinical Targets







7x daily fingersticks Target range 63-140 mg/dl Visits q4 weeks



CGM reduced hyperglycemia without increasing hypoglycemia

	CGM (n=159)	Control (n=156)	P-value
Mean glucose	121 +/- 16	126 +/- 20	0.14
% TIR	68 +/- 13	61 +/- 15	0.003
% TAR	27 (19, 37)	32 (25, 39)	0.028
% TBR	3 (1, 6)	4 (2, 8)	0.10

TIR, time in range (63-140 mg/dL); TAR, time above range; TBR, time below range

CGM resulted in 1.7 more hours per day spent in target range

CGM improved neonatal outcomes



Take Home Points

DM is a growing public health issue.

Repeat DM testing postpartum after GDM.

Insulin is first-line treatment. CGM shows promise for transforming diabetes care.



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