Are Oral Hypoglycemic Agents (OHA) effective in Gestational Diabetes Mellitus ?

Are Oral Hypoglycemic Agents effective in Gestational Diabetes Mellitus ?

Presented by –

Dr. Rubina Yasmin

FCPS

Assistant Professor

Dept of Medicine

Dhaka Medical College

The Confidential Enquiry into Maternal and Child Health (CEMACH) reported that women with diabetes mellitus (DM) have five times the risk of stillbirth, three times the risk of neonatal death and twice the risk of a major congenital anomaly than women in the general population.

- **GDM affects about 7% of the more than 4 million births occurring annually in the USA and is associated with both maternal and neonatal complications**

- **The guidelines of ACOG & ADA emphasize the importance of glucose control in GDM to promote maternal well-being and avoid adverse neonatal outcomes, such as macrosomia, birth trauma, and neonatal hypoglycemia.**

When dietary management fails to achieve adequate glucose control, an antihyperglycemic medication should be used.

Traditionally insulin has been considered the standard for management because of the ability to achieve tight maternal glucose control without the risk of transfer of insulin across the placenta.

An oral diabetes medication (i.e glyburide, metformin) is being used increasingly in women with GDM even though it has not been formally approved by the US FDA for this indication.

A total of 14,093 unique citations (14,064 from electronic databases and 29 from hand-searching) was retrieved.

Nine studies related to the benefits and harms of oral diabetes agents and insulin.

Three RCTs compared glyburide and insulin, with a total of 478 participants.

One RCT compared metformin and insulin (N751 participants.)

Five cohort studies with a total of 831 participants.

Characteristics of Randomized Controlled Trials Reporting on the Effects of Oral HypoglycemicAgents Compared With Insulin on Maternal and Neonatal Outcomes

	Study Characteristics					
Author	Treatment	OGTT/GA at Diagnosis (wk)	Age (y)	Race	Prepregnancy BMI	Gravida/Parity
Insulin vs glyburide						
Anjalakshi et al[16] 2006, India	I: 13	75-g WHO/I: 22.62	27.46	As: 13 (100)	25.32	NR
	G: 10	G: 22.5	24.9	As: 10 (100)	22.82	NR
Bertini et al[17] 2005, Brazil	I: 27	75-g WHO F: 110 mg/dL 2-h: 140 mg/dL	28.7	NR	27	2.5
	G: 24	NR	31.2	NR	27.5	3.2
	A: 19		31.5	NR	25.7	2.9
Langer et al[15,25] 2000,United States	I: 203	3-h OGTT* F: 95 mg/dL/I: 25	30	NR	BMI 27.3 or more 132 (65)	59 nullip
	G: 201	G: 24	29	NR	BMI 27.3 or more 141 (70)	56 nullip
Insulin vs metformin						
Rowan et al[18] 2008, Australia, New Zealand	I: 378		33.0±5.1	W: 168 (45) P: 83 (22) Ind: 55 (15) As: 37 (10) O: 27 (7)	NR	31.9% nullip
	M: 373	75-g WHO F: 110 mg/dL 2-h: 140 mg/dL	33.5±5.4	W: 175 (48) P: 73 (20) Ind: 38 (11) As: 49 (14) O: 28 (8)	NR	31.7% nullip

Effects of Oral Hypoglycemic Agents or Insulin on Maternal Outcomes (Insulin Compared With Glyburide): Randomized Controlled Trials

Author	Treatment	Preeclampsia	Cesarean Delivery	Weight (kg)	Glycemic Control During Pregnancy (mg/dL)	Hypoglycemia
Anjalakshi et al[16] 2006	G1: Insulin: 13				2-h PG: B 175±31; F 93±10	
	G2: Glibenclamide: 10				2-h PG: B 167±23; F 95±7	
Bertini et al[17] 2005	G1: Insulin: 27		12 (44)	Maternal F–B 11.5±3.8	FBG: B 108±26; F 96±16†	Requiring hospital admission: 0 (0)
	G2: Glyburide: 24		12 (50)	10±5.2		0 (0)
	G3: Acarbose: 19		10 (52)	10.6±3.2; *P*=.46*		0 (0)
					Preprandial glucose: B 107±23; F 97±14†	FSG less than 40 mg/dL 41 (20)
Langer et al[15] 2000	G1: Insulin: 203	12 (6)	49 (24)		2-h PPG: B 129±27; F 112±15†	
					Combined glucose: B 116±22‡; F 105±18	
					FBG: B 104±25; *P*=.12§; F 98±13†; *P*=.17§	
					Preprandial glucose: B 104±20; *P*=.16§; F 95±15†; *P*=.17§	FSG less than 40 mg/dL 4 (2); *P*=.03
	G2: Glyburide: 201	12 (6)	46 (23)		2-h PPG: B 130±25; *P*=.69§; F 113±22†; *P*=.6§	
					Combined glucose: B 114±19‡; *P*=.33§ F 105±16; *P*=.99§	
Rowan et al[18] 2008	G1: Metformin: 363	20 (5.5)	131 (36)	F–B 0.4±3	FBG†: 93.6±11) 2-h PPG: 111.6±11	
	G2: insulin: 370	26 (7.0)	142 (38) *P*=.5	F–B 2.0±3; *P*<.001	FBG†: 91.8±13; *P*=.24§ 2-h PPG: 115.2±16; *P*=.003	

Effects of Oral Hypoglycemic Agents or Insulin on Neonatal Outcomes: Randomized Controlled Trials

Author	Treatment	Hypoglycemia	Hyperbilirubinemia	Macrosomia
Insulin compared with glyburide				
Anjalakshi et al[16] 2006	G1: Insulin: 13 G2: Glibenclamide: 10			
Bertini et al[17] 2005	G1: Insulin: 27	Capillary glucose less than 40 mg/dL: 1 (4)		BWT more than 4,000 g: 0 (0)
	G2: Glyburide: 24	8 (33)		4 (16)
	G3: Acarbose: 19	1 (5) $P=.006$*		0 (0)
Langer et al[15] 2000	G1: Insulin: 203	Two consecutive blood glucose less than 40 mg/dL: 12 (6)	Serum bilirubin more than 12 mg/dL: 8 (4)	BWT more than 4,000 g: 9 (4)
	G2: Glyburide: 201	18 (9) $P=.25$†	12 (6) $P=.36$†	14 (7) $P=.26$†
Metformin compared with insulin				
Rowan et al[18] 2008	G1: Metformin: 363	Any blood glucose less than 28.8 mg/dL 12 (3.3)		
	G2: Insulin: 370	30 (8.1) RR 0.41 (0.21–0.78) $P=.008$		

LGA	SGA	Mortality	Other Outcome	Birth Weight (g)
PW more than 90: 63 (24); OR: Reference	PW less than 10: 18 (7); OR: Reference		NICU admission: 65 (24); OR: Reference Birth trauma, claims data/ICD-9 codes, total birth injuries: 3 (1) Congenital malformation, claims data/ICD-9 codes: 4 (2)	3,599±650
60 (25); OR 1.44, 95% CI 0.91–2.27	12 (6) OR 0.62, 95% CI 0.26–1.43		NICU admission: 35 (15) OR 0.57, 95% CI 0.34–0.93 Birth trauma, claims data/ICD-9 codes total birth injuries: 8 (3) Congenital malformation, claims data/ICD-9 codes: 4 (2)	3,661±629; *P*=.28*
				3,327±634
				3,267±815; *P*=.78*
		Fetal mortality: 0 (0)	NICU admission: 1 (8)	3,608±398
		Fetal mortality: 1 (2); *P*>.05*	NICU admission: 4 (7); *P*>.05*	3,430±714; *P*>.05*
			NICU admission: 2 (10); OR: Reference Shoulder dystocia: 2 (11) Shoulder dystocia: 7 (10); *P*=.932	3,319±559

Effects of Oral Hypoglycemic Agents or Insulin on Maternal Outcomes: Nonrandomized Controlled Trials and Observational Studies

Author	Treatment	Operative Delivery	Preeclampsia	Cesarean Delivery	Glycemic Control During Pregnancy (mg/dL)	Hypoglycemia
Jacobson et al[22] 2005	G1: Insulin in 1999–2000: 268	15 (6)	16 (6); OR Reference	Total cesarean deliveries: 94 (36)	FBG B: 105±13 F: 98±12 1-h PPG B: 223±29 F: 138±24 2-h PPG B: 197±34 F: 119±20	FBS less than 60 mg/dL: mean 19*
	G2: Glyburide in 2001–2002: 236	12 (5)	28 (12); OR 2.32 (95% CI 1.17–4.63)	91 (39)	FBG B: 103±14; P=.005† F: 90±13; P<.001† 1-h PPG B: 220±27; P=.48† F: 131±23; P<.001† 2-h PPG B: 195±32; P=.44†	Mean 50‡
Chmait et al[19] 2004	G1: Glyburide failure (glyburide+diet+insulin or insulin+diet): 13			Elective cesarean delivery: 1 (7.69) Elective cesarean delivery: 1 (7.69)	Fasting glucose§ 114±17 1-h PPG§ 145±20	
	G2: Glyburide success (glyburide+diet): 56			Elective cesarean: 4 (7.14) Total cesarean: 19 (34); P>.05†	Fasting glucose§ 88±11; P<.001* 1-h PPG§ 124±12; P<.001†	
Yogev et al[20] 2004	G1: Diet: 27				FBG B: 96±21 F: 99±13	FSG less than 50 mg/dL, symptoms, 30 or more consecutive without patient awareness: 0 (0)
	G2: Insulin: 30				FBG B: 99±23 F: 104±15	19 (63); P=.009‖; OR 4.4 (95% CI 1.4–13.9)
	G3: Glyburide: 25				FBG B: 98±27; P=0.17¶ F: 105±14; P=.24¶	7 (28); OR: Reference
Rochon et al[23] 2006	G1: Glyburide failure (NPH and regular insulin): 21			9 (43)		
	G2: Glyburide success (glyburide+diet): 80			30 (38)		

Effects of Oral Hypoglycemic Agents or Insulin on Neonatal Outcomes From Observational Studies

Author	Treatment	Hypoglycemia	Hyperbilirubinemia	Macrosomia
Jacobson et al[22] 2005	G1: Insulin in 1999–2000, 268	ICD-9-CM codes: 73 (27); OR: Reference	Serum bilirubin more than 12 mg/dL within first 7 d of birth: 58 (22); OR: Reference	BWT more than 4,000 g: 64 (24); OR: Reference
	G2: Glyburide in 2001–2002, 236	72 (31); OR 1.27, 95% CI 0.84–1.94	59 (25); OR 1.18, 95% CI 0.75–1.85	60 (25); OR 1.28, 95% CI 0.82–2
Conway et al[21] 2004	G1: Glyburide failure, 12			BWT more than 4,000 g: 1 (8)
	G2: Glyburide success, 63			7 (11) P=1.0*
Chmait etal[19] 2004	G1: Glyburide failure (glyburide+diet+insulin OR insulin+diet), 13	FSG less than 40 mg/dL: 0 (0.00)	Serum bilirubin more than 15 mg/dL: 1 (8.33)	BWT more than 4,000 g: 2 (10)
	G2: Glyburide success (glyburide+diet), 56	FSG less than 40 mg/dL: 1 (1.85)	Serum bilirubin more than 15 mg/dL: 2 (3.70)	BWT more than 4,000 g: 15 (18); P>.05*
Rochon et al[23] 2006	G1: Glyburide failure (NPH and regular insulin), 21	Any heel stick less than 40 mg/dL: 2 (10)	Requiring NICU admission: 0 (0)	BWT more than 4,000 g: 2 (11)

CONCLUSIONS

Oral glucose-lowering agents have generally not been recommended likely due to limited data on these agents.

The evidence from this report does not show any increased risks of harm associated with the use of glyburide, acarbose, or metformin, as compared with human insulin in the treatment of GDM, yet trial data were limited on several of these comparisons and on the outcomes reported.

These findings are particularly important because the use of these agents in pregnancy is still somewhat controversial.

THANK YOU