Universal Screening and Timely Intervention in Gestational Diabetes Mellitus: A Key to Successful Feto-Maternal Outcome

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AGENDA

- Recommendations for universal screening of GDM
- Recommendations for time of screening of GDM
- What happens if GDM is not treated?
- Effect of GDM on mother
- Effect of GDM on fetus
- Effect of treatment of GDM cases

GESTATIONAL DIABETES MELLITUS

Glucose intolerance of variable severity with onset or first recognition during pregnancy

GDM REDEFINED...

Overt / pre-gestational diabetes - Diagnosis of hyperglycemia in the first trimester as per non-pregnant cut-offs

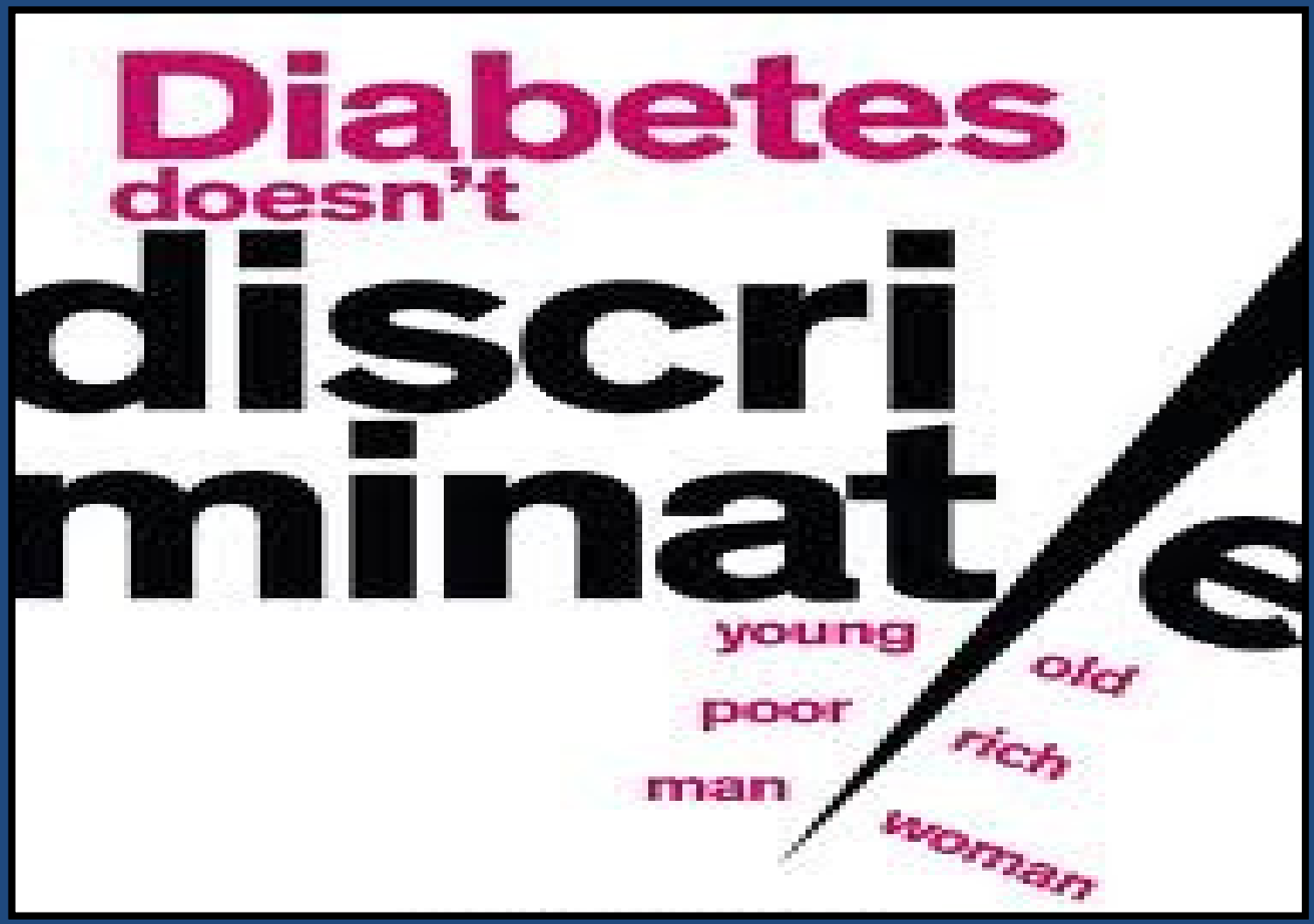
GDM - Diagnosis of hyperglycemia in the 2nd or 3rd trimester

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Endocrine Society 2013

WHO-2013: Hyperglycemia in pregnancy

FBS≥126 mg/dl and PGBS≥200 mg/dl : Diabetes in pregnancy(It is any time during pregnancy)


Diabetes
doesn't
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WHAT ABOUT GDM

- Whether it affects only high risk category women

- It can affect any one irrespective of the risk factors

- BMI>25 kg/m^2
- Physical inactivity
- First degree relative with DM
- High risk ethnicity (Asian American, Latino, African American etc)
- Delivery of baby weighing >9 lb or H/O GDM
- HTN, CVD, PCOD
- HDL<35 mg/dl or TGs>250 mg/dl

EVEN TODAY THE WORLD DIVIDES ON THE FOLLOWING ASPECTS OF GDM



- Universal screening or risk based screening?
- Time of screening:(First trimester and/or At 24-28 weeks of gestation)

WHOM TO SCREEN?

Universal screening

- ADA 2014
- WHO 2013
- ES 2013
- IADPSG 2010
- DIPSI 2006

RISK BASED SCREENING

- ACOG 2001
- NIH 2013

WHEN TO SCREEN

- The fetal beta cells recognise maternal serum glycemic level as early as 16th week of gestation.

Nahum GG, Wilson SB, Stanislaw H. Early-pregnancy glucose screening for gestational diabetes mellitus. *J Reprod Med 2002;47:656-62*

- The peak of insulin resistance is observed between 24th to 28th week of gestation.

WHEN TO SCREEN

GESTATIONAL AGE	IADPSG / ADA	DIPSI
1st trimester or 1st antenatal visit	Screen for type-2 DM in high risk group only with 75gm OGTT and interpret as non-pregnant OGTT values	Screen for GDM universally
24-28 weeks	**Screen for GDM**	**Screen for GDM if previous test normal**
32-34 weeks	----------	Screen for GDM if previous test normal

WHY THIS HUE AND CRY?



ITS BECAUSE OF TWO THINGS

- Very high prevalence of GDM
- Significant adverse feto-maternal outcome

PREVALENCE OF GDM- GLOBAL

- Global prevalence: 16.8% (21.4 million)

IDF REGION	Cases in live births MILLIONS	Prevalence* %
AFR	4.6	14.4
EUR	1.7	12.6
MENA	3.4	17.5
NAC	0.9	10.4
SACA	0.9	11.4
SEA	6.3	25.0
WP	3.7	11.9

*comparative prevalence

IDF diabetes atlas-2013

META-ANALYSIS FINDING OF VARIABLE PREVALENCE OF GDM ACROSS STUDIES AND DIAGNOSTIC CRITERIA

Hartling L et al	Review Methods	Prevalence of GDM
	The search identified 14,398 citations and included 97 studies (6 randomized controlled trials, 63 prospective cohort studies, and 28 retrospective cohort studies) between 1995 to May 2012	ADA(75gm): 2 to 19% Carpenter& Coustan: 3.6 to 38% NDDG: 1.4 to 50% WHO: 2 to 24.5%

Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Aktary WM, Pasichnyk D, Seida JC, Donovan L. Screening and diagnosing gestational diabetes mellitus. Evid Rep Technol Assess (Full Rep). 2012 Oct;(210):1-327.

INCREASING PREVALENCE – WHY?

- Change in life style
- Increasing prevalence of obesity & type 2 DM
- More women with pregnancy at advanced age
- More detection rate due to improved health care
- Lower cut offs for diagnosis and universal screening

IF GDM IS NOT TREATED

META-ANALYSIS TO SHOW OUTCOMES OF NON-TREATED GDM

Hartling L et al	REVIEW METHODS	RESULTS	CONCLUSION
	Thirty-eight studies examined health outcomes for women who met different criteria for GDM and did not undergo treatment	Methodologically strong studies showed a continuous positive relationship between increasing glucose levels and the incidence of primary CS and macrosomia. One study also found significantly fewer cases of preeclampsia, CS, shoulder dystocia and/or birth injury, clinical neonatal hypoglycemia, and hyperbilirubinemia for women without GDM compared with those meeting IADPSG criteria	Evidence supports a positive association with increasing plasma glucose on a 75 g /100 g OGTT and macrosomia and primary CS, clear thresholds for increased risk were not found

Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Aktary WM, Pasichnyk D, Seida JC, Donovan L. Screening and diagnosing gestational diabetes mellitus. Evid Rep Technol Assess (Full Rep). 2012 Oct;(210):1-327

EFFECTS OF GDM ON MOTHER

PERIPARTUM

- Pre-eclampsia
- Polyhydramnios
- Preterm labour
- Operative delivery

LONG TERM

- Type 2 DM
- CVD
- Metabolic syndrome

EFFECTS OF GDM ON FETUS

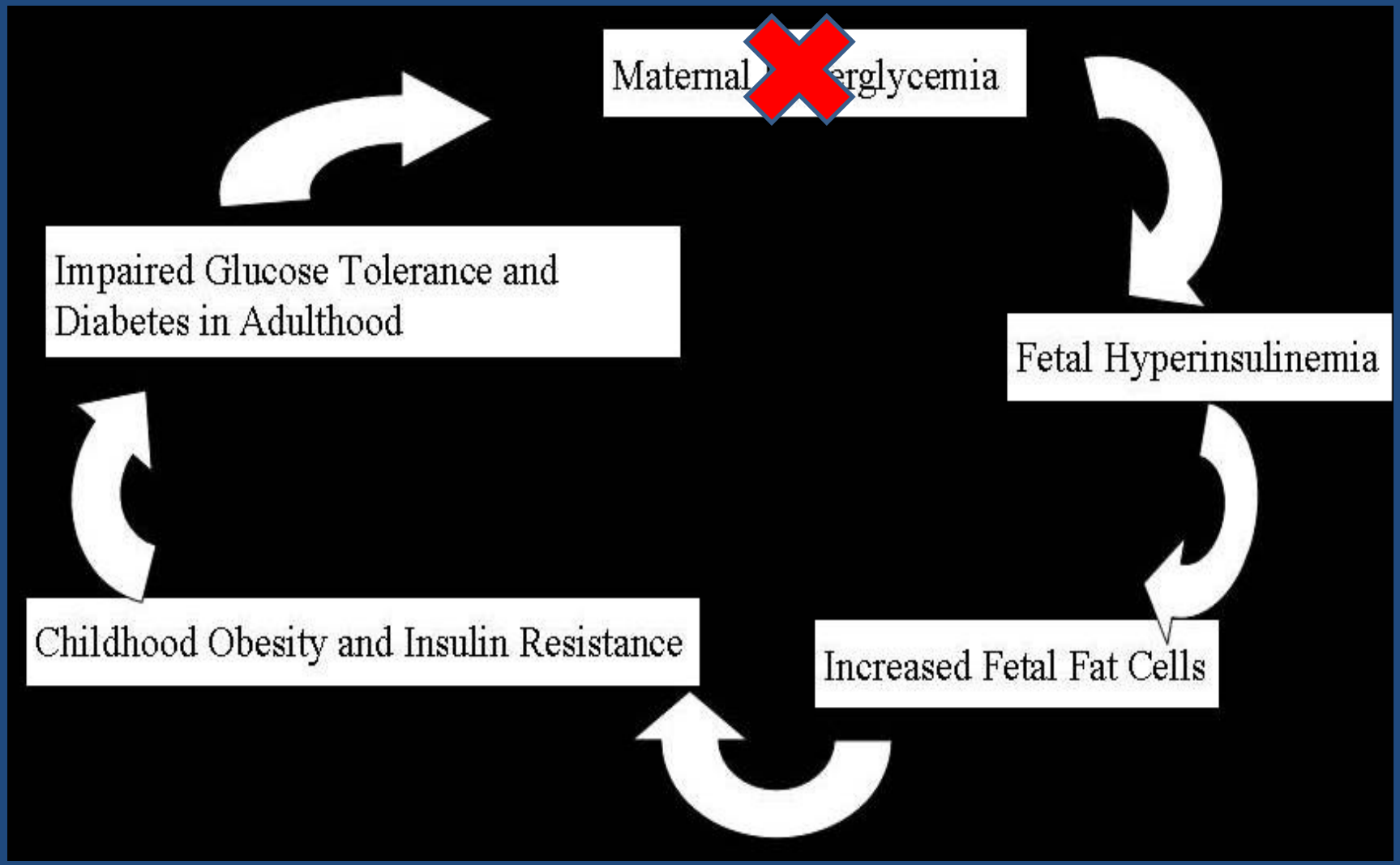
PERINATAL

- Macrosomia
- IUGR
- Organomegaly
- Shoulder dystocia
- Birth trauma
- RDS
- Hypoglycemia
- Hyperbilirubinemia
- Abortion or sudden IUFD

LONG TERM

- Obesity
- Type-II DM
- CVD
- Impaired cognitive development
- Impaired motor function

GDM & ITS LEGACY - VICIOUS CYCLE



WHETHER ADVESRSE PREGNANCY OUTCOMES IN GDM IS INDEPENDENT OF OTHER RISK FACTORS?

STUDY	NUMBER OF PATIENTS	STUDY OUTCOME
Metzger et al(HAPO study)	25505	GDM complications are independent of other confounding factors(Age,BMI,Mean BP,Parity,smoking,Height,Family Hist)
Sermer M et al	4274	Increasing maternal carbohydrate intolerance associated with a graded increase in adverse maternal and fetal outcome
Schmidt MI et al	4977	GDM predicts adverse pregnancy outcomes
Sacks DA et al	3505	Positive association between maternal blood glucose and birth weight percentiles

- Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR et al. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine 2008; 358(19):1991-2002.*
- Sermer M, Naylor CD, Farine D, Kenshole AB, Ritchie JW, Gare DJ et al. The Toronto Tri-Hospital Gestational Diabetes Project. A preliminary review. *Diabetes Care 1998; 21 Suppl 2:B33-B42.*

EVIDENCE TO SHOW ADVERSE EFFECTS OF GDM ON MOTHER

EVIDENCE TO SHOW GDM AS A RISK FACTOR FOR PREECLAMPSIA

STUDY	NO. OF PATIENTS	STUDY OUTCOME
Schmidt MI et al	4977	GDM associated with adverse pregnancy outcomes including preeclampsia
Metzer BE et al	25505	Among the secondary outcomes strongest associations was found for preecclampsia

- Schmidt MI, Duncan BB, Reichelt AJ, Branchtein L, Matos MC, Costa e Forti et al. Gestational diabetes mellitus diagnosed with a 2-h 75-g oral glucose tolerance test and adverse pregnancy outcomes. *Diabetes Care 2001; 24(7):1151-1155.*

- Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR et al. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine 2008; 358(19):1991-2002.*

EVIDENCE TO SHOW GDM AS A RISK FACTOR FOR CAESAREAN DELIVERY

STUDY	NO. OF PATIENTS	STUDY OUTCOME
Sugaya A et al	416	GDM significantly increased caesarean section rate
Metzer BE et al	25505	Significant increase in caesarean section rate as a primary outcome
Aberg A et al	4526	Significant increase in caesarean delivery among women with a glucose tolerance value between 140-162 mg/dl

- Sugaya A, Sugiyama T, Nagata M, Toyoda N. Comparison of the validity of the criteria for gestational diabetes mellitus by WHO and by the Japan Society of Obstetrics and Gynecology by the outcomes of pregnancy. *Diabetes Research and Clinical Practice 2000; 50(1):57-63*

- Aberg A, Rydhstroem H, Frid A. Impaired glucose tolerance associated with adverse pregnancy outcome: a population-based study in southern Sweden. *American Journal of Obstetrics and Gynecology 2001; 184(2):77-83.*

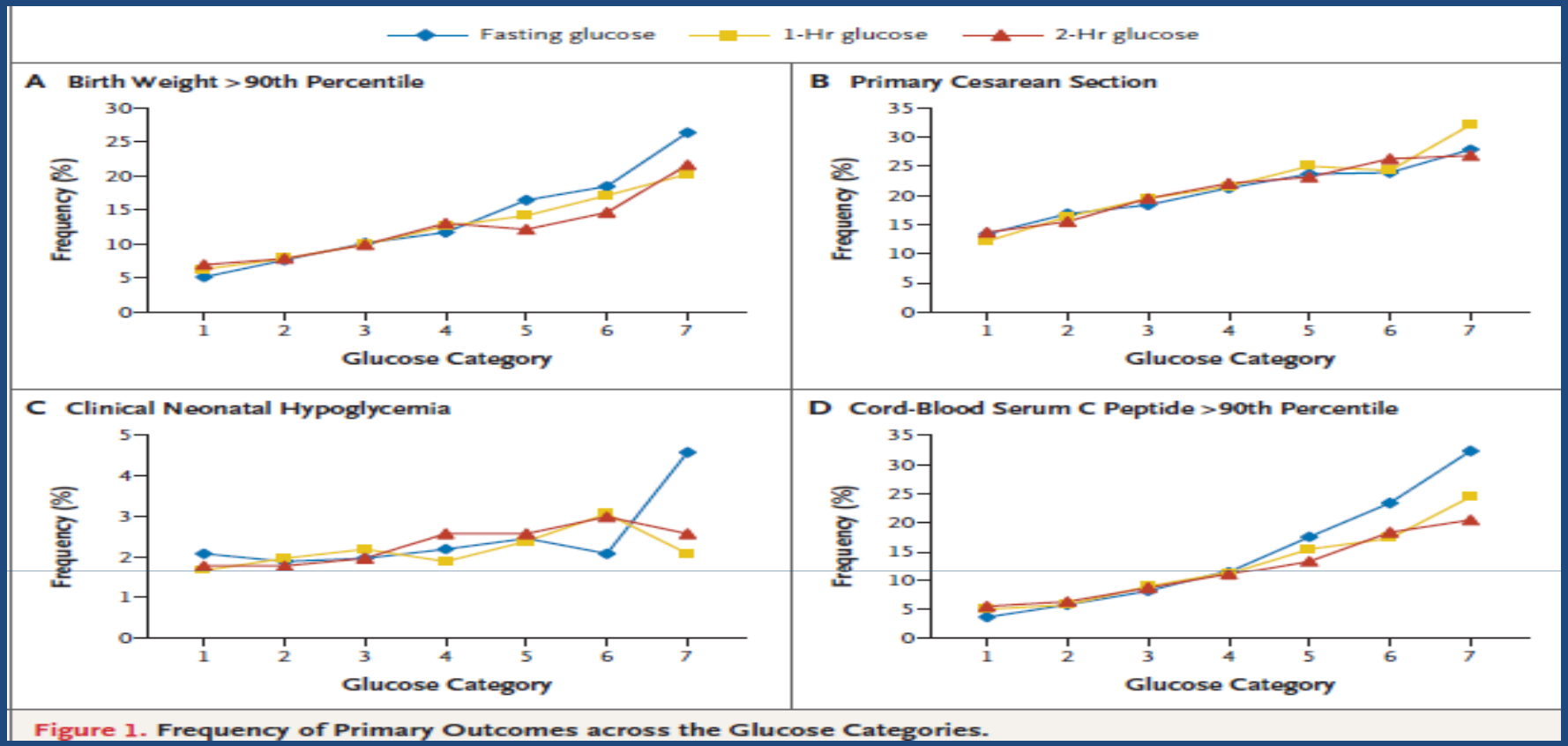


Figure 1. Frequency of Primary Outcomes across the Glucose Categories.

The study by Moses et al and the HAPO study showed a dose-response gradient across maternal glucose levels for the various adverse pregnancy outcomes

- Moses RG, Calvert D. Pregnancy outcomes in women without gestational diabetes mellitus related to the maternal glucose level. Is there a continuum of risk? *Diabetes Care 1995; 18(12):1527-1533*

HIGHLIGHTS OF ADVERSE MATERNAL OUTCOME IN FUTURE

- 30-84 % chances of recurrence; most significantly influenced by race with higher risk in nonwhite race/ethnicity[1]
- 7-fold increased risk of developing type 2 DM in future[2]
- Increased risk for cardiovascular diseases & metabolic syndrome[3]

[1]Kim C, Newton KM, Knopp RH: Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care 2002,25(10):1862–1868.

[2]Bellamy L, Casas J, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet 2009;373(9677):1773–9.

[3]Sullivan SD, Umans JG, Ratner R. Gestational diabetes: implications for cardiovascular health. Current Diabetes Reports 2012;12(1):43–52.

SYSTEMATIC REVIEW TO FIND THE PREDICTORS OF FUTURE TYPE-II DM AMONG GDM MOTHERS

STUDY	RESULT	CONCLUSION
Golden SH et al(2009)	5 out of 11 studies showed that FBG, in the antepartum OGTT is a significant predictor of future T2DM(odds ratio [OR] range: 11.1-21.0; relative risk [RR] range: 1.37-1.5; relative hazard [RH] = 2.47). Risk of incident T2DM was predicted by the antepartum 2-hour OGTT plasma glucose in 3 studies (OR range: 1.02-1.03; RR = 1.3) and by the antepartum OGTT glucose AUC in 3 other studies (OR range: 3.64-15; RH = 2.13).	FBG, OGTT 2-hour blood glucose, and OGTT glucose AUC appeared to be strong and consistent predictors of subsequent T2DM among women who met diagnostic criteria for GDM using the OGTT

Golden SH, Bennett WL, Baptist-Roberts K, Wilson LM, Barone B, Gary TL, Bass E, Nicholson WK. Antepartum glucose tolerance test results as predictors of type 2 diabetes mellitus in women with a history of gestational diabetes mellitus: a systematic review. Gend Med. 2009;6 Suppl 1:109-22

GDM AS A CAUSE OF CARDIOVASCULAR DISEASES IN MOTHER

- Pre-eclampsia is a novel cardiovascular risk marker.
- Pre-eclampsia increases both the long term risk of cardiovascular disease and the risk that it will occur earlier.

- *Magee, L. A., and P. Von Dadelszen. "Pre-eclampsia and increased cardiovascular risk." BMJ 335.7627 (2007): 945-946.*
- *Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. British Medical Journal 2007; 335(7627):974*

META-ANALYSIS FOR PREECLAMPSIA AS A RISK FACTOR OF CARDIOVASCULAR DISEASE AND CANCER IN LATER LIFE

Bellamy L et al	Review methods	RESULTS	CONCLUSIONS
	Prospective and retrospective cohort studies were included, providing a dataset of 3,488,160 women, with 198,252 affected bypre-eclampsia (exposure group) and 29,495 episodes of cardiovascular disease and cancer (st udy outcomes)	The RR (95% CI) for HTN were 3.70 (2.70 to 5.05) after 14.1 yrs weighted mean follow-up, for IHD 2.16 (1.86 to 2.52) after 11.7 years, for stroke 1.81 (1.45 to 2.27) after 10.4 years, and for VTE 1.79 (1.37 to 2.33) after 4.7 years. No increase in risk of any cancer was found (0.96, 0.73 to 1.27), including breast cancer (1.04, 0.78 to 1.39) 17 years after pre-eclampsia	A history of PE should be considered when evaluating risk of CVD in women. This association might reflect a common cause for PE and CVD, or an effect of PE on disease devel opment, or both. No association was found between PE and future cancer

Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007 Nov 10;335(7627):974

ADVERSE EFFECTS OF GDM ON FETUS

INTRA UTERINE FETAL PROGRAMMING

Gestational programming is a process whereby stimuli or stresses that occur at critical or sensitive periods of fetal development, permanently change structure, physiology, and metabolism, which predispose individuals to disease in adult life

- ***Lucas A (1991) Programming by early nutrition in man. In: Bock GR, Whelan J (eds) The childhood environment and adult disease. John Wiley and Sons, Chichester (UK), pp 38 - 55***

GESTATIONAL PROGRAMMING AND FUTURE DIABETES MELLITUS

- Epigenetic regulation of gene expression: Through this mechanism, genetic susceptibility and environmental insults can lead to Type-II DM
- T2D is a disorder of complex genetics influenced by interactions between susceptible genetic loci and environmental perturbations such as IUGR.
- An abnormal metabolic intrauterine milieu affects fetal development by permanently modifying expression of key genes regulating β-cell development (*Pdx1*) and glucose transport (*Glut4*) in muscle

- Pinney SE, Simmons RA. Epigenetic mechanisms in the development of type 2 diabetes. *Trends in Endocrinoly and Metabolism2010; 21(4):223-229*

GESTATIONAL PROGRAMMING AND OTHER HEALTH DISORDERS OF OFFSPRINGS IN FUTURE

- Poor health in utero leads to poor pregnancy outcomes, which in turn lead to poor health in childhood(1)
- Young children with poor health are, in turn, at higher risk for serious conditions in adulthood such as obesity and cardiovascular disease (1)
- Altered placental perfusion, may contribute to the development of long term adverse outcomes in the offspring(2)

- *1.Barker, D. J. (2004). The developmental origins of adult disease. Journal of the American College of Nutrition, 23, 588S-595S - See more at: http://earlysuccess.org/resources/health#sthash.u3rtOMGw.dpuf*
- *2.Barker DJ. Adult consequences of fetal growth restriction. Clinical Obstetrics & Gynecology 2006; 49(2):270-283*

EVIDENCE TO SHOW ASSOCIATION OF MACROSOMIA IN GDM

STUDY	NO.OF PATIENTS	STUDY OUTCOME
Aberg A et al	4526	Macrosomia associated with GDM
Black MH et al (Retrospective study)	9835	Overweight and GDM together leads to LGA babies
Wendland EM et al(Review article)	44829	GDM consistently associated with macrosomia and LGA babies when WHO diagnostic criteria was used

- Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, Campos MA et al. Gestational diabetes and pregnancy outcomes - a systematic review of the World Health Organization (WHO) and the International ion of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. *BMC Pregnancy Childbirth 2012; 12(1):23.*
- Aberg A, Rydhstroem H, Frid A. Impaired glucose tolerance associated with adverse pregnancy outcome: a population-based study in southern Sweden. *American Journal of Obstetrics and Gynecology 2001; 184(2):77-83.*
- Black MH, Sacks DA, Xiang AH, Lawrence JM. Clinical outcomes of pregnancies complicated by mild gestational diabetes mellitus differ by combinations of abnormal oral glucose tolerance test values. *Diabetes Care 2010; 33(12):2524-2530.*

EVIDENCE TO SHOW GDM AND PERINATAL MORTALITY AND MORBIDITY

Study	No of Patients	Results
Wendland EM et al(cohort)	4401	In settings of limited detection and treatment of gestational diabetes mellitus, women across a spectrum of lesser than diabetes hyperglycemia, experienced a continuous rise in perinatal death with increasing levels of glycemia after 34 weeks of pregnancy
Dodd JM et al(cohort)	16975	With increasing plasma glucose values, there is a significant increase in shoulder dystocia and neonatal hypoglycemia
Nayak PK et al (cohort)	304	NICU admission of neonates of GDM mothers were significantly higher

- Wendland EM, Duncan BB, Menge SS, Schmidt MI. Lesser than diabetes hyperglycemia in pregnancy is related to perinatal mortality: a cohort study in Brazil. *BMC Pregnancy Childbirth 2011; 11(1):92.*
- Dodd JM, Crowther CA, Antoniou G, Baghurst P, Robinson JS: Screening for gestational diabetes: The effect of varying blood glucose definitions in the prediction of adverse maternal and infant health outcomes. Aust Nz J Obstet Gyn 2007, 47(4):307–312
- Nayak PK, Mitra S, Sahoo JP, et al. Feto-maternal Outcomes inWomen with and without gestational diabetes mellitus according tothe International Association of Diabetes and Pregnancy StudyGroups (IADPSG) diagnostic criteria. Diabetes Metab Syndr 2013;7:206–9

GDM AND LONG TERM FETO-MATERNAL ADVERSE OUTCOME

Study	No.of Patients	Result of Study
O' Sullivan JB et al	615	Only one trial showing no association of future diabetes even 16 years after GDM.
Gillman MW et al	199	Treatment of mild GDM did not affect BMI at age 4-5 years

There is lack of data to show long-term effects of GDM treatment on offspring morbidity and to show the effect of treatment on the improvement of maternal outcomes in later life

- O'Sullivan JB, Mahan CM, Charles D, Dandrow RV. Medical treatment of the gestational diabetic. *Obstetrics & Gynecology 1974; 43(6):817-821.*
- Gillman MW, Oakey H, Baghurst PA, Volkmer RE, Robinson JS, Crowther CA. Effect of treatment of gestational diabetes mellitus on obesity in the next generation. *Diabetes Care 2010; 33(5):964-968.*

OUR EXPERIENCE

GYNECOLOGICAL ENDOCRINOLOGY

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ORIGINAL ARTICLE

Predictors for antenatal insulin requirement in gestational diabetes

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Abstract

The purpose of this study was to identify pre-gestational and gestational factors predicting subsequent insulin requirement in patients with gestational diabetes mellitus (GDM). Maternal parameters were compared between mothers achieving glycemic control with or without the addition of antenatal insulin therapy (AIT). Insulin was required only in 8/83 (10%) patients for glycemic control. Those who needed insulin had a stronger family history of diabetes and higher first hour plasma glucose along with multiple (>1) abnormal values during oral glucose tolerance test (OGTT) in univariate analysis ($p < 0.05$). The first hour plasma glucose value of ≥9.72 mmol/l predicted requirement of AIT in GDM mothers with a sensitivity of 100% and specificity of 73%. However, only positive family history of diabetes mellitus among first degree relatives and multiple abnormal values in OGTT were independent predictors for antenatal insulin requirement in regression analysis.

Keywords

Body mass index, gestational diabetes, insulin

History

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CAN TREATMENT FOR GDM REDUCE ADVERSE PREGNANCY OUTCOMES

STUDY	RCT(Int.GP/ Control GP)	EFFECTS OF TREATMENT
ACHOIS TRIAL Crowther CA et al	490/510	Rate of serious perinatal complications(Perinatal mortality, shoulder dystocia, birth trauma etc) reduced and so also macrosomia, LGA and hypertensive disorders
Landon MB et al	485/473	Treatment of mild GDM reduces the risks of LGA,Shoulder dystocia,caesarean delivery and hypertensive disorders
Falavigna et al	Systematic review with 7 studies	Treatment of GDM significantly reduced the risk of macrosomia, LGA, shoulder dsystocia(allocation concealment was clearly specified in above two studies)

- Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *New England Journal of Medicine 2005; 352(24):2477-2486.*
- Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *New England Journal of Medicine 2009; 361(14):1339-1348.*
- Falavigna M, Schmidt MI, Trujillo J, Alves LF, Wendland ER, Torloni MR et al. Effectiveness of gestational diabetes treatment: a systematic review with quality of evidence assessment. Diabetes Research and Clinical Practice. In press 2012

DIAGNOSING AND TREATING GESTATIONAL DIABETES PROVIDES

"An opportunity to prevent feto-maternal complications during pregnancy and after pregnancy"