

Gestational diabetes mellitus:

Short term and long term effect on child's health

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Historical background in GDM

- Definition – Carbohydrate intolerance first recognized in pregnancy
- History – first appeared in the literature in 1950's
- O'Sullivan & Mahan – based on $+2SD > \bar{x}$ glucose level at 0, 1, 2, 3 h of a 100 g OGTT
 - Increase in long term outcome
 - But not address to pregnancy outcome

Controversies in GDM

- A physiological change v.s. a disease category
 - Should we treat GDM?
 - What should be the diagnostic criteria?

Landmark studies on GDM

1. HAPO study
 2. ACHIOS trial
 3. Maternal Fetal Medicine Network study
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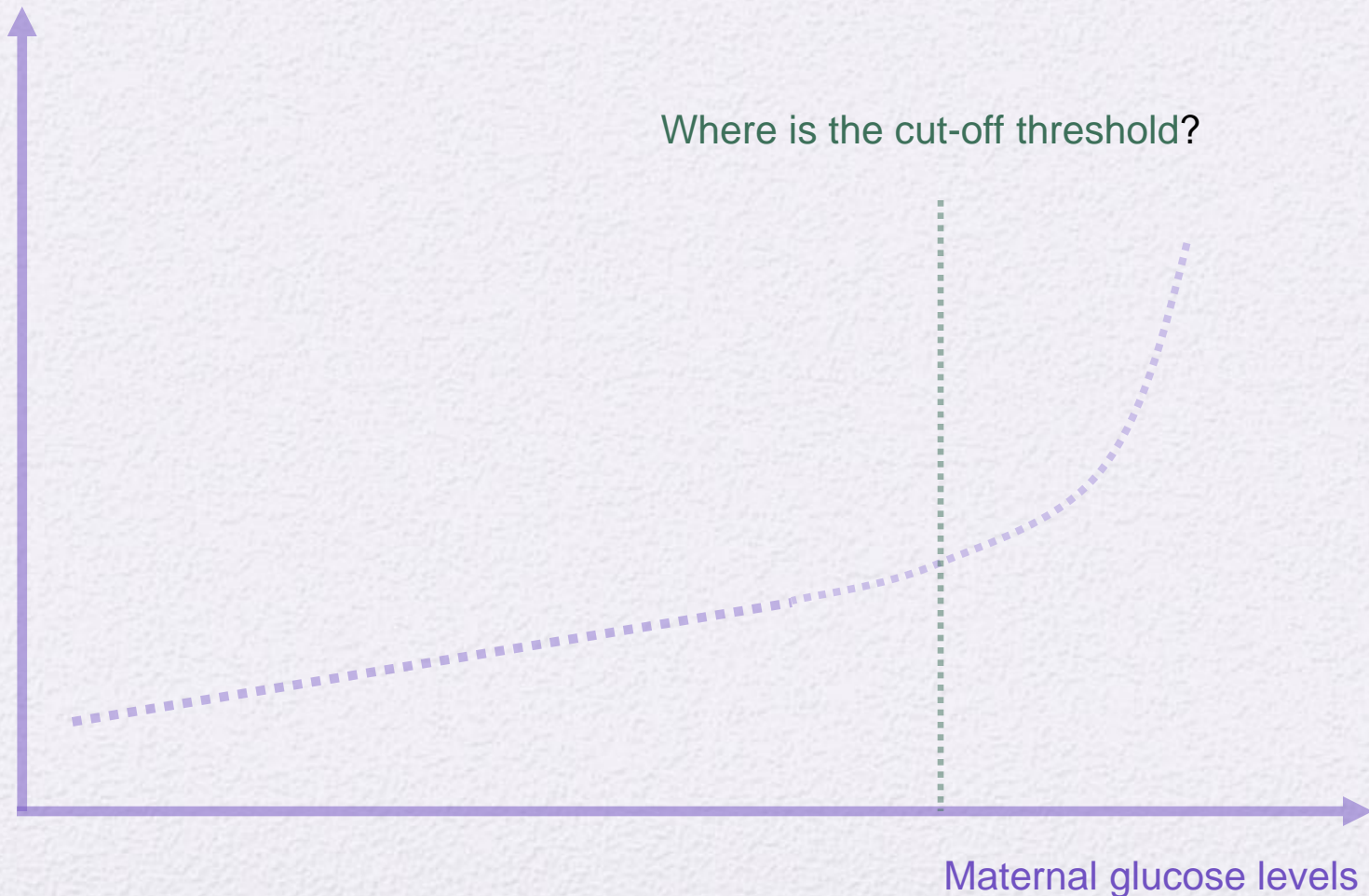
Hyperglycemia and Adverse Pregnancy Outcomes

The HAPO Study Cooperative Research Group*

- Multicentre multinational blinded study
 - 25,505 pregnant women
 - 15 centres
 - 9 countries, including HK

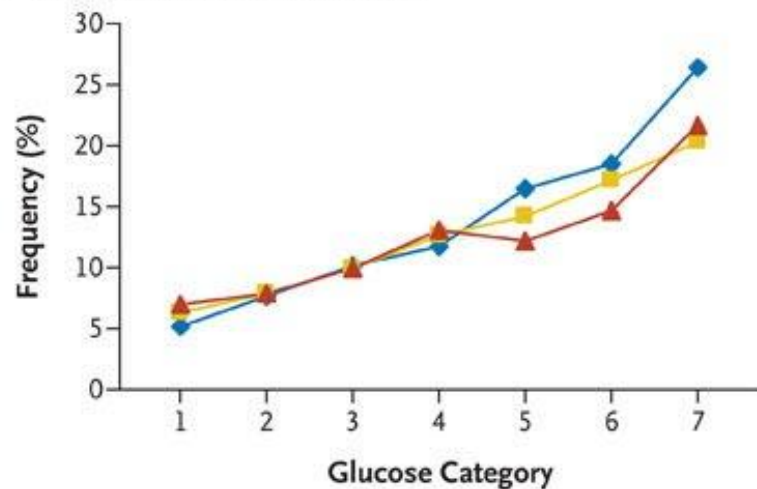
Hypothesis : Is there a curvilinear relationship between maternal hyperglycemia & adverse pregnancy outcome?

Adverse pregnancy outcomes (macrosomia, neonatal hypoglycemia, IUD etc ...)

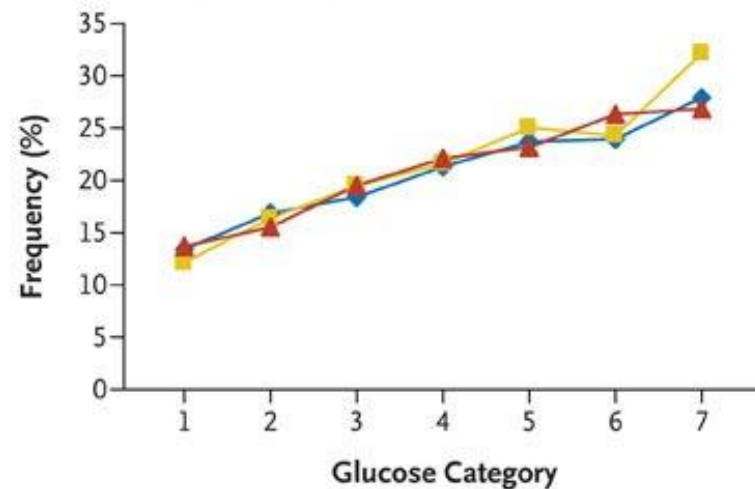


◆ Fasting glucose
 ■ 1-Hr glucose
 ▲ 2-Hr glucose

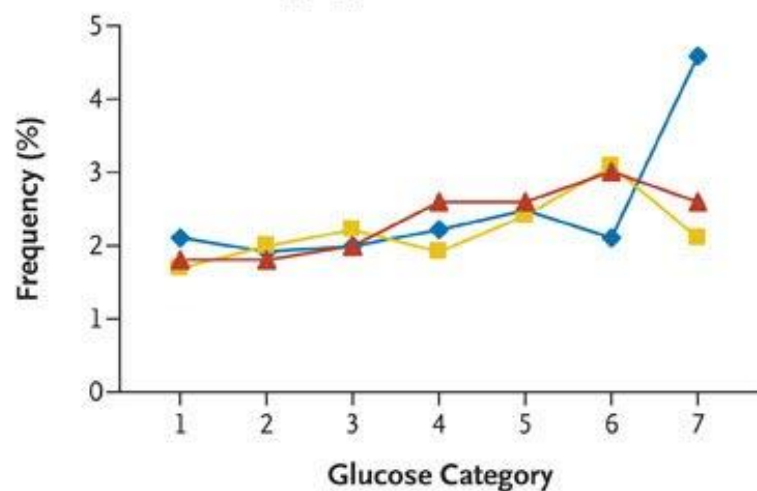
A Birth Weight >90th Percentile



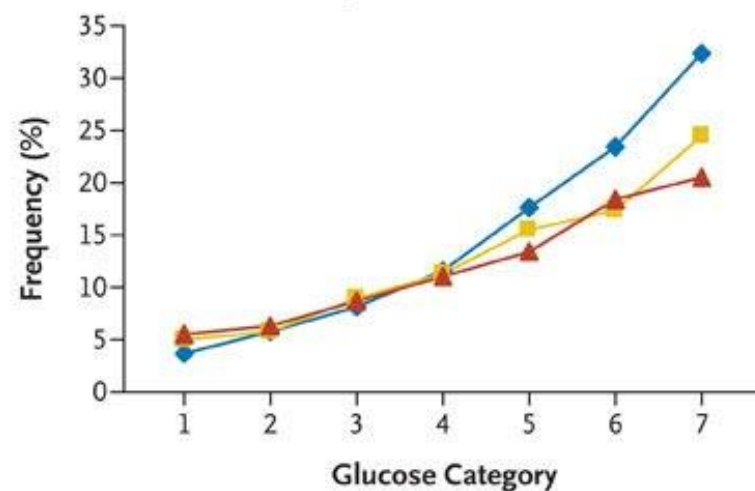
B Primary Cesarean Section



C Clinical Neonatal Hypoglycemia



D Cord-Blood Serum C Peptide >90th Percentile



DIABETES

Criteria for the diagnosis and treatment of gestational diabetes mellitus—time for a change

Landon and co-investigators call for a re-evaluation of current criteria for the diagnosis and treatment of gestational diabetes mellitus. Adverse maternal–fetal outcomes were observed at glucose levels below the current cutoffs for the diagnosis of the disease in their recent research.

Debate rages on the benefits of screening and treatment for gestational diabetes mellitus and on what constitutes appropriate thresholds for the diagnosis of the disease. Although evidence that has amassed in the past few years lends support to the argument that the risk of adverse perinatal outcomes could be reduced by diagnosis and treatment (even for mild gestational diabetes mellitus) questions still remain. Landon *et al.* aimed to inform the debate by examining the relationship between differing degrees of maternal hyperglycemia and perinatal outcomes, including macrosomia.

glycemic status for a composite of adverse perinatal outcomes (including hypoglycemia, perinatal mortality, hyperbilirubinemia, birth trauma and elevated cord blood C-peptide level) and for separate adverse perinatal outcomes, including an increased frequency of babies born large for gestational age. Furthermore, an abnormal glucose challenge test result of ≥ 7.5 mmol/l significantly increased the risk of the composite perinatal outcome and of babies being born large for gestational age.

Importantly, similar frequencies of some perinatal outcomes were found for the group with one abnormal OGTT result as for the group with untreated gestational diabetes mellitus. These results reinforce previous evidence to suggest that the presence of one abnormal OGTT should be considered in criteria for the diagnosis of the disease.

Next, the researchers looked for trends



Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study

- International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel

New criteria in the diagnosis of GDM

- FPG ≥ 5.1 mmol/L, or
- 1-h PG ≥ 10 mmol/L, or
- 2-h PG ≥ 8.5 mmol/L

Relationship between maternal glucose/BMI & PET (secondary analysis of HAPO study)

- higher fasting **C-peptide** is an independent predictor of **PET**, after adjustment for BMI and fasting glucose
- higher **maternal BMI** is associated with greater risk for **PET**, with the odds of PET ↑ ~8-fold from the lowest to highest category of BMI
 - **Maternal obesity** is a stronger risk factor for **PET**

Relationship between BMI & pregnancy outcome (secondary analysis of HAPO study)

- Higher maternal **BMI**, independent of maternal glycaemia, is strongly associated with ↑ frequency of pregnancy complications, in particular those related to **excess fetal growth** and **adiposity**

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Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes

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for the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group*

- Treatment of mild GDM (WHO criteria of IGT)
 - ↓ serious perinatal complications: death, shoulder dystocia, bone fracture, nerve palsy

ACHOIS trial

Table 2. Primary Clinical Outcomes among the Infants and Their Mothers.*

Outcome	Intervention Group <i>no. (%)</i>	Routine-Care Group	Unadjusted Relative Risk (95% CI)	Unadjusted P Value	Adjusted Relative Risk (95% CI) [†]	Adjusted P Value [‡]	Step-Down Sidak P Value
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	
Admission to neonatal nursery ^{**} 	357 (71)	321 (61)	1.15 (1.05–1.26)	0.002	1.13 (1.03–1.23)	0.01	0.04
Jaundice requiring phototherapy	44 (9)	48 (9)	0.95 (0.64–1.40)	0.79	0.93 (0.63–1.37)	0.72	0.98
Women							
Total no.	490	510					
Induction of labor ^{††} 	189 (39)	150 (29)	1.31 (1.10–1.56)	0.002	1.36 (1.15–1.62)	<0.001	0.003
Cesarean delivery	152 (31)	164 (32)	0.96 (0.80–1.16)	0.70	0.97 (0.81–1.16)	0.73	0.98
Elective	72 (15)	61 (12)	1.23 (0.89–1.69)	0.20	1.17 (0.85–1.60)	0.33	
Emergency	80 (16)	103 (20)	0.81 (0.62–1.05)	0.11	0.87 (0.68–1.13)	0.31	

Secondary analysis of ACHOIS trial

- Positive association between maternal fasting hyperglycaemia & risk of shoulder dystocia
- Every 1 mmol/l \uparrow in fasting glucose
 - RR 2.09 (95% CI 1.03-4.25)

Cost analysis (ACHIOS trial)

- For every 100 women with a singleton pregnancy & positive OGTT who were offered treatment for mild GDM in addition to routine obstetric care
 - \$53,985 additional direct costs were incurred at the obstetric hospital
 - \$6,521 additional charges were incurred by women and their families
 - 9.7 additional women experienced induction of labour
 - 8.6 more babies were admitted to a neonatal nursery
- 2.2 fewer babies experienced serious perinatal complication & 1.0 fewer babies experienced perinatal death
 - The **incremental cost** per additional serious perinatal complication prevented was **\$27,503**
 - per **perinatal death** prevented was **\$60,506** &
 - per discounted **life-year gained** was **\$2,988**

ORIGINAL ARTICLE

N ENGL J MED 361;14 NEJM.ORG OCTOBER 1, 2009

A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes

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Ronald J. Wapner, M.D., Michael W. Varner, M.D., Dwight J. Rouse, M.D.,
John M. Thorp, Jr., M.D., Anthony Sciscione, D.O., Patrick Catalano, M.D.,
Margaret Harper, M.D., George Saade, M.D., Kristine Y. Lain, M.D.,
Yoram Sorokin, M.D., Alan M. Peaceman, M.D., Jorge E. Tolosa, M.D., M.S.C.E.,
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Medicine Units Network*

- Treatment of mild GDM
 - ↓ LGA, macrosomia, shoulder dystocia, CS,
PET & GH

National Institute of Child Health and Human Development Maternal Fetal Medicine (NICHD MFMU Network) study

Table 3. Secondary Neonatal Outcomes.*

Outcome Variable	Treatment Group (N=485)	Control Group (N=473)	Relative Risk (97% CI)	P Value
Birth weight — g	3302±502.4	3408±589.4		<0.001
Birth weight >4000 g — no./total no. (%)	28/477 (5.9)	65/454 (14.3)	0.41 (0.26–0.66)	<0.001
Large for gestational age — no./total no. (%)†	34/477 (7.1)	66/454 (14.5)	0.49 (0.32–0.76)	<0.001
Fat mass — g	427.0±197.9	464.3±222.3		0.003
Preterm delivery — no./total no. (%)‡	45/477 (9.4)	53/455 (11.6)	0.81 (0.53–1.23)	0.27
Small for gestational age — no./total no. (%)§	36/477 (7.5)	29/455 (6.4)	1.18 (0.70–1.99)	0.49
Admission to NICU — no./total no. (%)	43/477 (9.0)	53/455 (11.6)	0.77 (0.51–1.18)	0.19
Intravenous glucose treatment — no./total no. (%)	25/475 (5.3)	31/455 (6.8)	0.77 (0.44–1.36)	0.32
Respiratory distress syndrome — no./total no. (%)	9/477 (1.9)	13/455 (2.9)	0.66 (0.26–1.67)	0.33

National Institute of Child Health and Human Development Maternal Fetal Medicine (NICHD MFMU Network) study

Table 4. Maternal Outcomes.*

Outcome Variable	Treatment Group (N=476)	Control Group (N=455)	Relative Risk (97% CI)	P Value
Induction of labor — no. (%)	130 (27.3)	122 (26.8)	1.02 (0.81–1.29)	0.86
Cesarean delivery — no. (%)	128 (26.9)	154 (33.8)	0.79 (0.64–0.99)	0.02
Shoulder dystocia — no. (%)	7 (1.5)	18 (4.0)	0.37 (0.14–0.97)	0.02
Preeclampsia — no. (%)	12 (2.5)	25 (5.5)	0.46 (0.22–0.97)	0.02
Preeclampsia or gestational hypertension — no. (%)	41 (8.6)	62 (13.6)	0.63 (0.42–0.96)	0.01
Body-mass index at delivery†	31.3±5.2	32.3±5.2		<0.001
Weight gain — kg‡	2.8±4.5	5.0±3.3		<0.001

Summary

- Continuous association between mild hyperglycaemia and adverse pregnancy outcome
- Treatment of GDM in addition to routine antenatal care reduce adverse pregnancy outcome: shoulder dystocia, macrosomia, CS, PET, fetal death
- Extra cost to prevent one case of serious perinatal complication and perinatal death
 - prevent 1 serious perinatal complication: HK\$ 220,000
 - prevent 1 perinatal death: HK\$ 484,000



Effect of GDM on children offspring

1. International study

Offspring of mothers who had DM in pregnancy

- Pima Indians:
 - Offspring born to mothers who had type 2 DM during pregnancy has higher risk of developing DM than to those mothers who developed it after the index pregnancy

Pettit et al. Diabetes 1988
Dabelea et al. Diabetes 2000
Dabelea & Pettit. J Ped Endocrin Metab 2001

- Prevalence of adolescent obesity – higher in offspring exposed in utero to maternal DM as compared to offspring of non-DM mother

Pettit et al. N Engl J Med 1983

↑ DM susceptibility (offspring of GDM mother)

- Retrospective study design
- Absence of a control group

Persson et al. Acta Paediatr Scand 1984

Dorner et al. Exp Clin Endocrinol 1987

Van Assche et al. Baillieres Clin Obstet Gynaecol 1991

Plagemann et al. Diabetologia 1997

Harder et al. Diabetes Care 2000

↑ Metabolic syndrome risk if born LGA

- Metabolic syndrome
 - 3 x at the age of 7
 - 4 x at the age of 9 } (compared to AGA at birth)
- Obesity at 11 of age – strong predictor of insulin resistance



Effect of GDM on children offspring

2. Local study

Glucose Intolerance and Cardiometabolic Risk in Children Exposed to Maternal Gestational Diabetes Mellitus in Utero

Wing Hung Tam, MBChB^a, Ronald Ching Wan Ma, MRCP^b, Xilin Yang, PhD^b, Gary Tin Choi Ko, MD^c, Peter Chun Yip Tong, PhD^b, Clive Stewart Cockram, MD^b, Daljit Singh Sahota, PhD^a, Michael Scott Rogers, MBChB, MD^a, Juliana Chung Ngor Chan, MD^b

At 8 years of age		NGT (n=101)	Gestational diabetes (n=63)	<i>p</i>
Body weight at the follow-up (kg)*		28.2 (0.7)	28.1 (0.9)	0.92
Waist circumference (cm)*		56.1(0.7)	56.9 (0.9)	0.51
Body mass index (BMI) (kg/m ²)*		16.2 (0.3)	16.2 (0.4)	0.86
Obesity	Waist circumference ≥85 percentile	24 (23.3)	14 (22.2)	0.87
	BMI ≥ 85 percentile	26 (25.5)	19 (30.2)	0.51
Systolic blood pressure (mmHg)*		88 (0.9)	94 (1.2)	<0.001
Diastolic blood pressure (mmHg)*		57 (0.6)	62 (0.8)	<0.001

Glucose Intolerance and Cardiometabolic Risk in Children Exposed to Maternal Gestational Diabetes Mellitus in Utero

Wing Hung Tam, MBChB^a, Ronald Ching Wan Ma, MRCP^b, Xilin Yang, PhD^b, Gary Tin Choi Ko, MD^c, Peter Chun Yip Tong, PhD^b, Clive Stewart Cockram, MD^b, Daljit Singh Sahota, PhD^a, Michael Scott Rogers, MBChB, MD^a, Juliana Chung Ngor Chan, MD^b

At 8 years of age		NGT (n=101)	Gestational diabetes (n=63)	<i>p</i>
Children's glycemic status	IFG	2 (2)	1 (1.6)	0.86
	IGT	1 (1)	1 (1.6)	
	DM	1 (1)	0	
Fasting plasma glucose (mmol/L) *		4.7 (0.04)	4.7 (0.06)	0.78
2hr-plasma glucose (mmol/L) *		5.2 (0.09)	5.4 (0.12)	0.29
HDL-C (mmol/L)*		1.71 (0.03)	1.58 (0.04)	0.019
LDL-C (mmol/L)*		2.5 (0.08)	2.7 (0.1)	0.08
Triglyceride (mmol/L)*		0.92 (0.04)	0.83 (0.06)	0.27
Total cholesterol (mmol/L)*		4.6 (0.08)	4.7 (0.1)	0.62

Multivariate logistic regression

		Abnormal glucose tolerance in the offspring	Odds ratio (95% CI)
Cord blood insulin level	≤ 90th percentile	3 (3.1 %)	8.9 (1.08-72.7)
	> 90th percentile	2 (20 %)	
Maternal gestational diabetes status	NGT	4 (4.0 %)	0.36 (0.03-3.8)
	GDM/GIGT	2 (3.2%)	
Macrosomia at birth	< 4 kg	5 (3.2 %)	6.12 (0.21-182)
	≥ 4 kg	1 (11.1%)	
Children's waist circumference at follow up	≥ 85th percentile	5 (3.9 %)	1.4 (0.14-14.3)
	< 85 th percentile	1 (2.7%)	
Mothers' glycaemic status at follow up	Normal	4 (3.3 %)	0.49 (0.02-10.3)
	IGR/DM	2 (5.6%)	

Glucose Intolerance and Cardiometabolic Risk in Adolescents Exposed to Maternal Gestational Diabetes

A 15-year follow-up study

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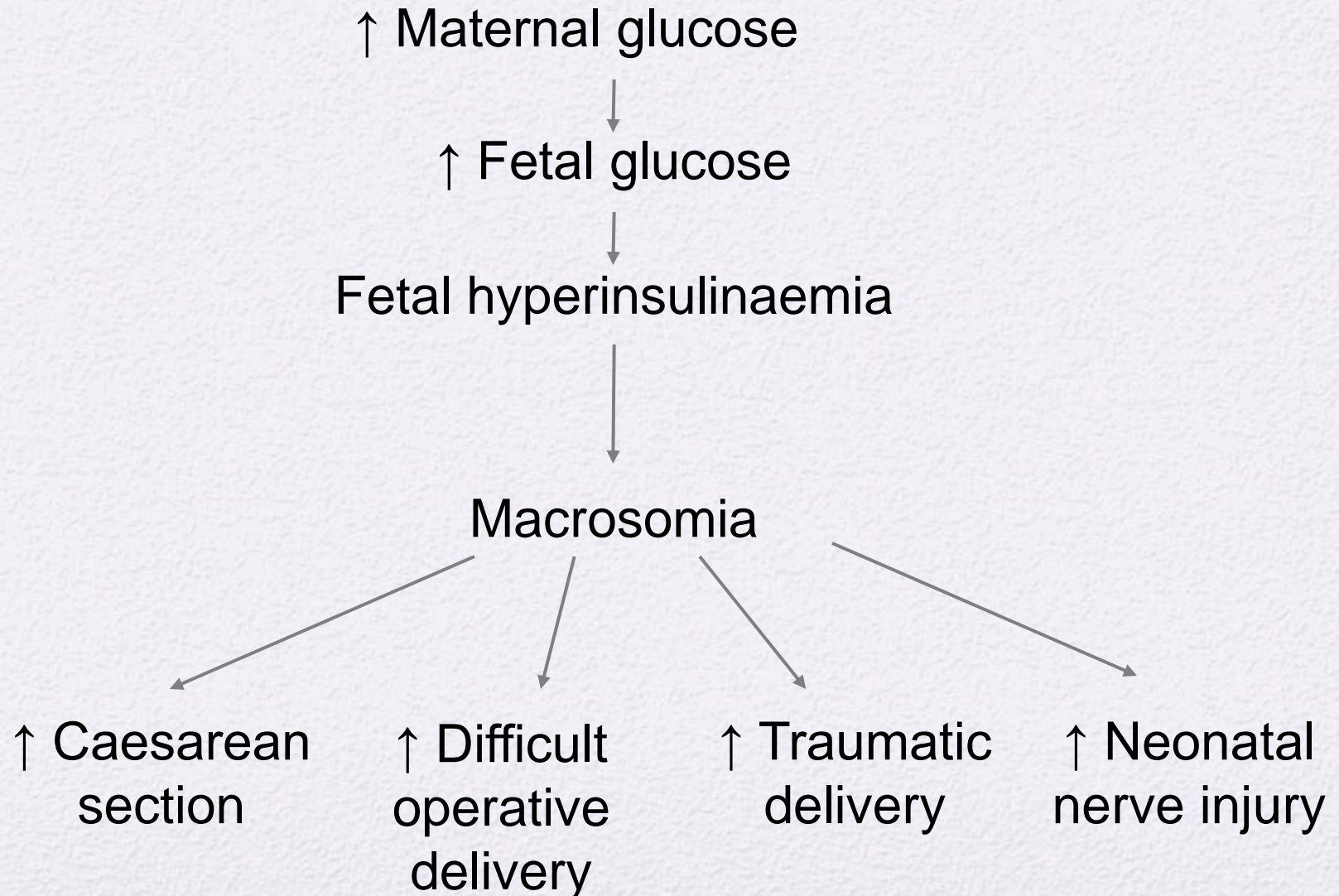
ALICE PIK SHAN KONG, FRCP²
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Hyperinsulinaemia

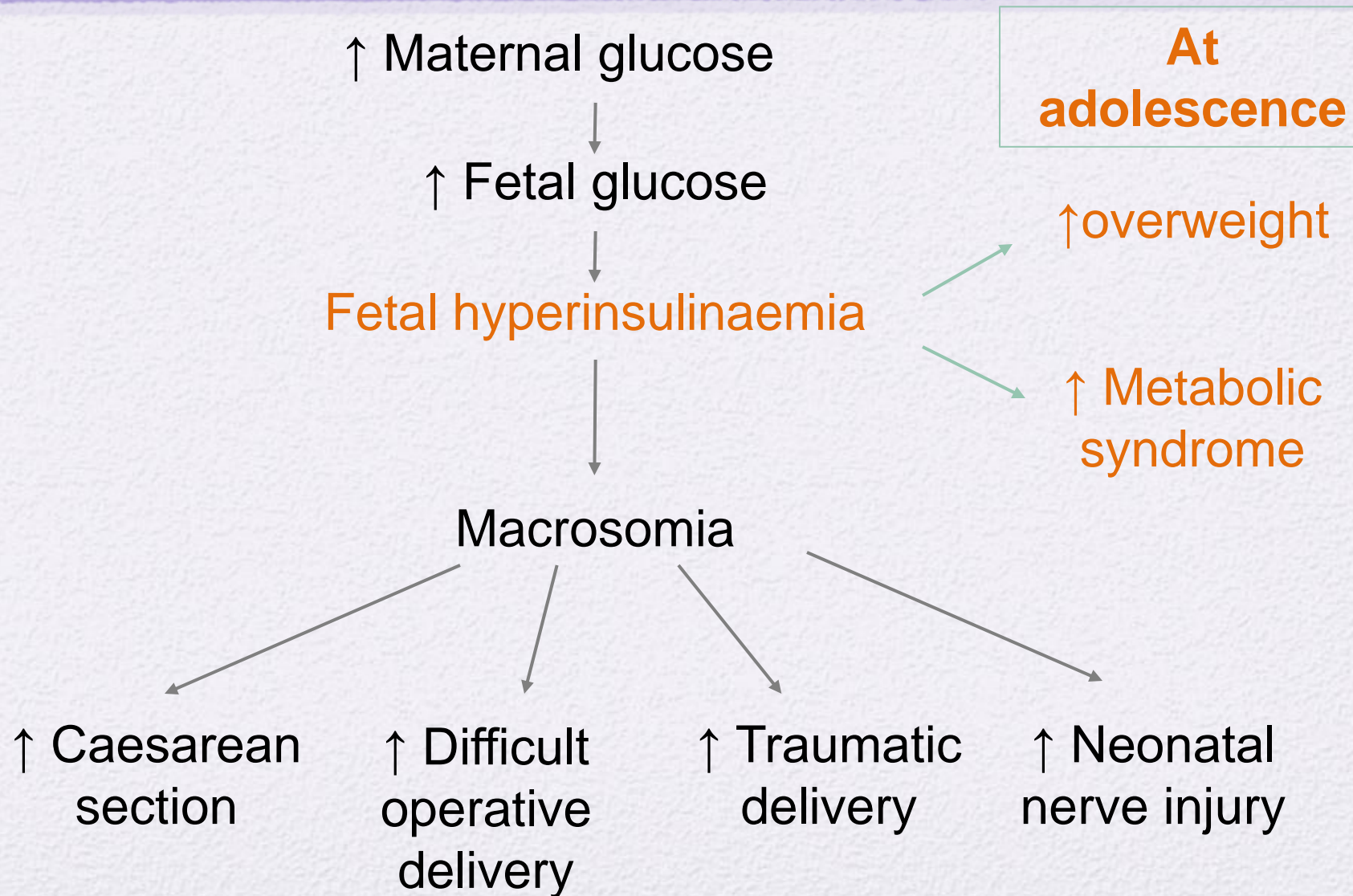
Odds ratio

Umbilical cord	Hyperinsulinaemia		Odds ratio
	C peptide > 90 th percentile	C peptide < 90 th percentile	
Metabolic syndrome	22.2%	2.7%	17.6
Overweight	44.4%	13.7%	10.8

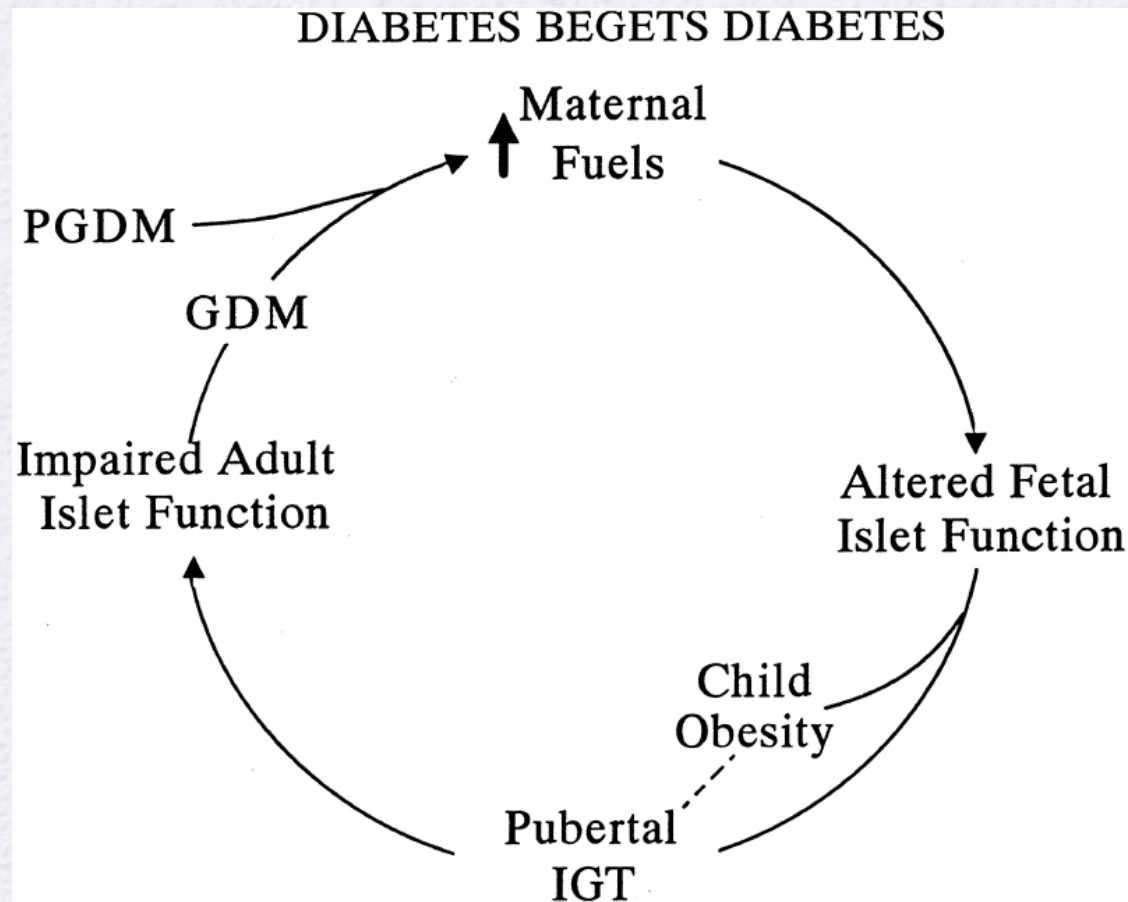
Complication of GDM in pregnancy



Additional risk of hyperinsulinaemia



Diabetes Begets Diabetes



HAPO – FU study (at 6 year post-delivery)

- Subjects: all Chinese HAPO study subjects & their children
- Mothers:
 - Anthropometric indices & BP, LFT, lipid profile, urinalysis
 - 75gram OGTT (Fasting, 2 hour)
- Children:
 - Anthropometric indices & BP, LFT, lipid profile, urinalysis
 - 5 point OGTT 1.75 g/kg (glucose + insulin levels)

Mother's cardio-metabolic risk at 6 year (HAPO – FU)

Maternal glycaemic status in pregnancy		NGT (N=628)	GDM (N=136)	<i>p</i>
Age		37.5 ± 4.6	39.5 ± 4.4	< 0.001
BMI		22.9 ± 3.6	24.0 ± 3.4 ↑	0.001
SBP		110 ± 11	113 ± 11 ↑	0.01
DBP		71 ± 9.6	73 ± 9.0 ↑	0.04
Hypertension		38 (5.8%)	10 (7.9%)	0.36
Glycaemic status at follow up	IFG/IGT	59 (9.0%)	35(28%) ↑	<0.001
	DM	2 (0.3%)	9 (7.2%) ↑	
Already diagnosed DM		0	2 (1.6%)	-
HDL		1.6 ± 0.4	1.5 ± 0.3 ↓	0.006
TG		0.97 ± 0.76	1.18 ± 0.88 ↑	0.01
TC		4.8 ± 0.8	5.0 ± 0.8 ↑	0.02
HDL < 1.03		19 (2.9%)	5 (4.0%)	0.52
TG ≥ 1.7		67 (10.2%)	19 (15.1%)	0.11

Children's cardio-metabolic risk at 6 year(HAPO – FU)

Maternal glycaemic status in pregnancy		NGT (N=668)	GDM (N=136)	<i>p</i>
Age		7.0 ± 0.5	6.9 ± 0.5	0.04
Male: Female		353:316	63:73	0.17
BMI		15.0 ± 2.3	15.3 ± 2.3	0.9
SBP		102 ± 8.9	104 ± 9.0↑	0.05
DBP		62 ± 7.8	63 ± 8.2	0.09
Glycaemic status at follow up	IFG/IGT	10 (1.5%)	6 (4.5%)↑	0.01
	DM	-	1 (0.8%)↑	
PG (0 min)		4.6 ± 0.3	4.6 ± 0.5	0.21
PG (15 min)		7.1 ± 1.2	7.2 ± 1.4	0.27
PG (30 min)		7.5 ± 1.5	7.9 ± 1.6↑	0.01
PG (60 min)		5.8 ± 1.5	6.3 ± 1.7↑	0.003
PG (120 min)		5.3 ± 1.0	5.4 ± 1.0	0.6

Children's cardio-metabolic risk at 6 year(HAPO – FU)

Children's glycaemic status		NGT (N=739)	AGT (N=16)	<i>p</i>
Age		7.0 ± 0.5	6.9 ± 0.4	0.43
% of Male		51.5%	56.2%	0.71
BMI		15.0 ± 2.2	16.6 ± 4.4	0.17
SBP		102 ± 8.6	105 ± 13	0.37
DBP		62 ± 7.8	65 ± 10.3	0.10
Maternal GDM (IADPSG criteria)		119 (16.1%)	6 (37.5%) [†]	0.023
Maternal glycaemic status at follow up	IFG/IGT	89 (12%)	3 (18.8%)	0.18
	DM	10 (1.4%)	1 (6.2%)	
Maternal BMI at follow up		23.2 ± 3.5	24.0 ± 4.3	0.35
Maternal age at follow up		37.8 ± 4.6	37.8 ± 4.4	0.94

Effect of maternal hyperglycaemia in pregnancy to children's AGT

- UNIANOVA
 - Maternal fasting glucose and 1st hour glucose are independent predictor of children's AGT after adjusting maternal AGT, BMI, children's sex & age

Maternal glucose levels at OGTT during pregnancy	Children's odds of having AGT	P
Fasting glucose \geq 5 mmol/L	1.6	0.017
1 st h glucose \geq 10 mmol/L	1.4	0.025
2 nd glucose \geq 8.5 mmol/L	1.2	0.042

* adjusted for maternal age, BMI, present glycaemic status, children's age & sex



Situation of GDM on Hong Kong

Prevalence of GDM in Hong Kong

Table 1—Frequency of GDM by field center (IADPSG criteria) and participants with elevated FPG, 1-h PG, and 2-h PG

Center*	Participants/ center	Percent GDM	Percent of GDM diagnosed by each glucose measure			Percent of all women with individual glucose measures \geq threshold			Percent of women with GDM with individual glucose measures \geq threshold		
			FPG†	1-h PG‡	2-h PG§	FPG	1-h PG	2-h PG	FPG	1-h PG	2-h PG
HAPO overall	23,957	17.8	55	33	12	9.8	9.7	6.7	55	55	38
Bellflower, CA	1,981	25.5	73	21	6	18.7	12.4	6.9	73	49	27
Singapore, Singapore	1,787	25.1	47	39	14	11.9	16.3	11.7	47	65	47
Cleveland, OH	797	25.0	64	27	10	15.9	12.0	9.4	64	48	38
Manchester, U.K.	2,376	24.3	67	26	7	16.2	13.8	8.5	67	57	35
Bangkok, Thailand	2,499	23.0	24	64	12	5.5	17.4	10.0	24	76	43
Chicago, IL	753	17.3	53	28	19	9.2	8.0	8.0	53	46	46
Belfast, U.K.	1,671	17.1	63	30	7	10.7	7.8	4.2	63	46	25
Toronto, Canada	2,028	15.5	66	24	9	10.3	7.5	5.2	66	48	34
Providence, RI	757	15.5	73	19	9	11.2	5.9	5.3	73	38	34
Newcastle, Australia	668	15.3	64	25	11	9.7	7.2	5.7	64	47	37
Hong Kong, PRC	1,654	14.4	26	45	29	3.8	8.9	9.4	26	62	65
Brisbane, Australia	1,444	12.4	50	31	18	6.2	5.9	4.8	50	47	39
Bridgetown, Barbados	2,093	11.9	74	9	17	8.8	3.8	5.1	74	32	43
Petah-Tiqva, Israel	1,818	10.1	43	45	13	4.3	6.3	3.4	43	62	33
Beersheba, Israel	1,631	9.3	57	28	15	5.3	3.8	2.4	57	41	26

PG, plasma glucose; PRC, People's Republic of China. *Centers listed from highest to lowest unadjusted frequency of GDM. †Includes all with FPG \geq threshold without regard to 1-h and 2-h value. ‡Includes all with FPG < threshold and 1-h \geq threshold without regard to 2-h value. §Only 2-h value is \geq threshold.

Lack of consensus

- No unified diagnostic criteria
- No unified screening strategy
 - OGTT once v.s. OGTT twice (mothers with risk factors)
 - Spot glucose as screening test
- No standardized treatment criteria
 - Treatment for all GDM v.s. no treatment for <9 mmol/L (2nd h glucose) or no treatment for <10 mmol/L (2nd h glucose)

Different protocols

Hospitals	75g OGTT cut-off		Remark
	IGT	GDM	
A	-	FPG ≥ 5.5 or 2hPG ≥ 8.0	accept also IADPSG criteria if 1hPG available
B	-	FPG ≥ 7.0 or 2hPG ≥ 7.8	
C	-	FPG ≥ 7.0 or 2hPG ≥ 7.8	
D	FPG < 7.0 & 2hPG 7.8 - 11.0	FPG ≥ 7.0 or 2hPG ≥ 11.1	
E	FPG < 7.0 & 2hPG 7.8 - 11.0	FPG ≥ 7.0 or 2hPG ≥ 11.1	
F	FPG < 7.0 & 2hPG 7.8 - 11.0	FPG ≥ 7.0 or 2hPG ≥ 11.1	
G	FPG ≥ 5.5 & < 7.0 2hPG 7.8 - 11.0	FPG ≥ 7.0 or 2hPG ≥ 11.1	
H	FPG ≥ 6.0 or 2hPG ≥ 9.0 (dietary treatment)	FPG ≥ 7.0 or 2hPG ≥ 11.1	no treatment if 2hPG 8-9 unless presence of risk factors: e.g. PCOS, HT, previous GDM..

Scale of problem

- 40,000 local pregnant population/year
- GDM = 14.4% = 5,760
- Risk of DM (0.8%) and pre-diabetic (4.5%)
= 42 type II DM + 252 IGT/IFG /per year
- Majority would have been missed without diagnosis of mother and antenatal intervention

Summary

- Preliminary HAPO FU data: increase risk of IGT and DM among the offspring
- All were unrecognized
- Majority of the mothers whose DM and IGT also not diagnosed prior to the study FU
- Future work:
 - whether prenatal treatment will reduce the risk?
 - whether postnatal surveillance and lifestyle modification of the children will reduce the risk?
 - the cost-effectiveness of screening and treatment on impact of the postnatal life?



Thank you
