

2017 대한내분비학회 제4회

WEB SYMPOSIUM



대한내분비학회

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WEB SYMPOSIUM

Speaker

김 신 곤 교수
(고려의대 안암병원)

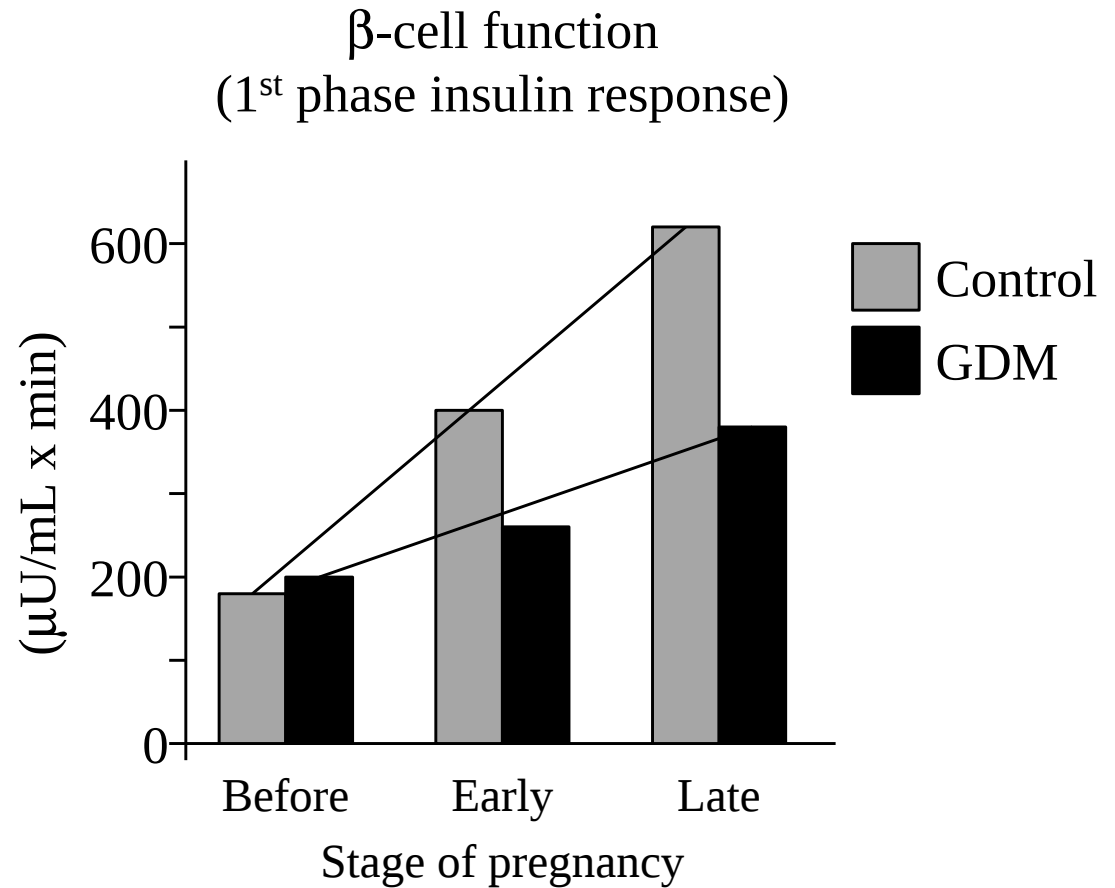
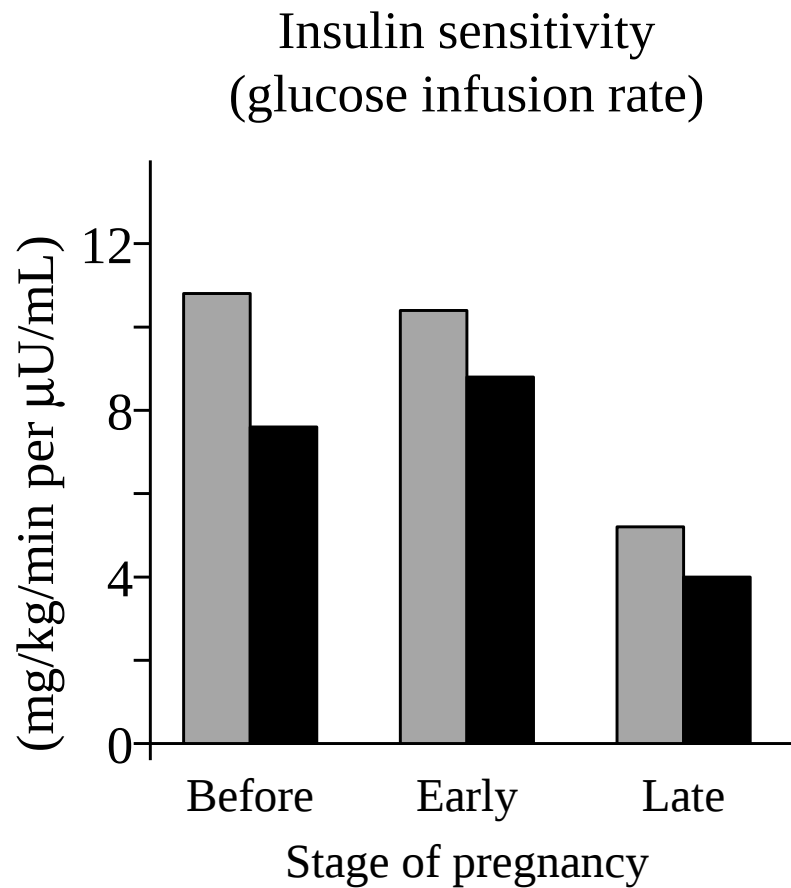
학력/경력

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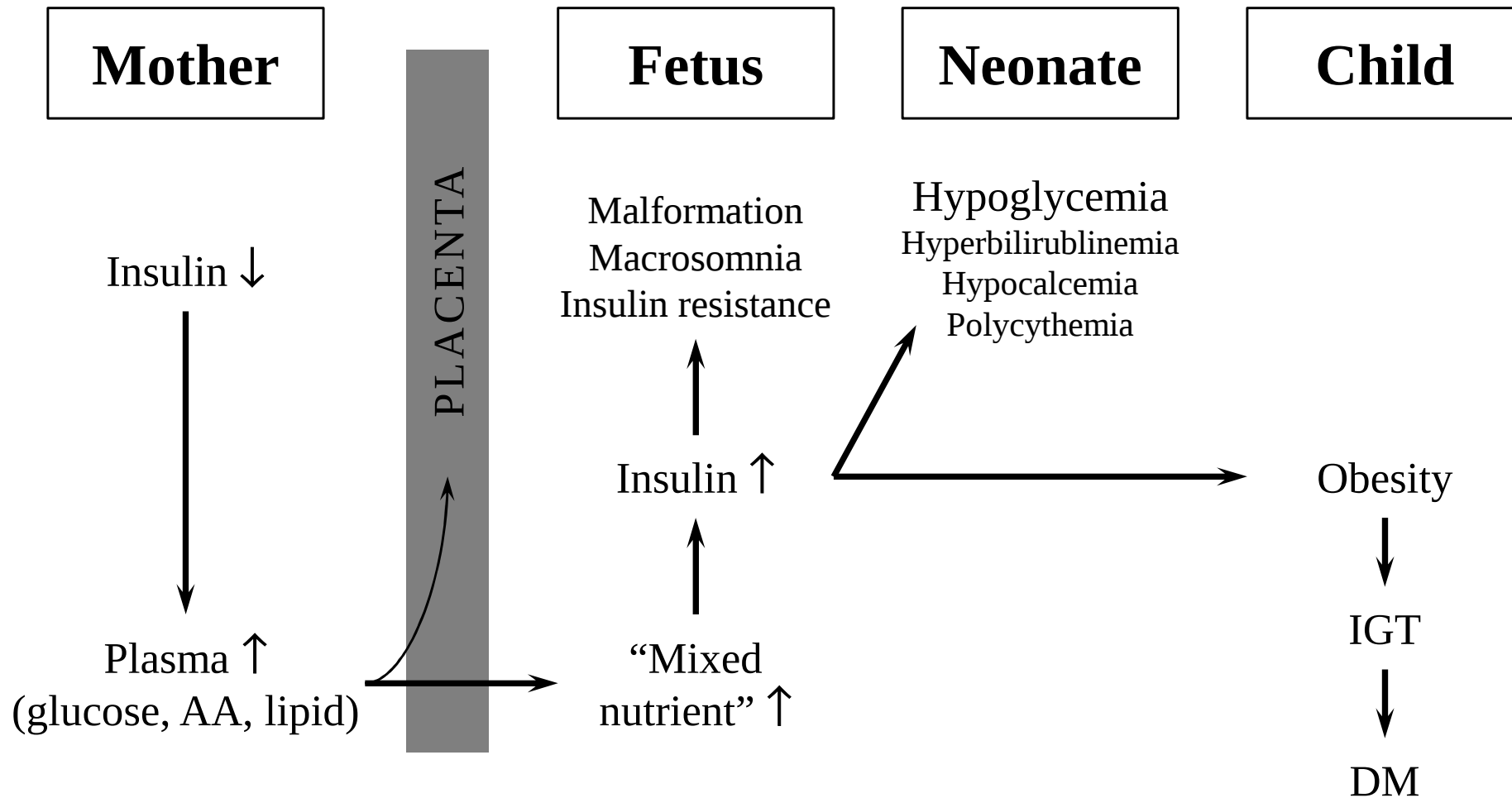
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현 대한내분비학회 학술이사

임신성 당뇨병

임신 중 인슐린 감수성/분비능 변화



Pedersen/Freinkel hypothesis



Prevalence of GDM in Korea

HIRA database

Table 1. Prevalence rate of gestational diabetes mellitus (GDM) between 2009 and 2011.

Age (years)	2009			2010			2011			P-values
	Total pregnancies	Cases with GDM*	Prevalence, %	Total pregnancies	Cases with GDM*	Prevalence, %	Total pregnancies	Cases with GDM*	Prevalence, %	
Total	479,160	27,491	5.7	449,747	34,954	7.8	377,374	35,958	9.5	<0.001
<20	3,766	31	0.8	4,150	59	1.4	4,173	74	1.8	0.358
20–24	27,436	722	2.6	24,457	864	3.5	21,699	874	4.0	0.011
25–29	169,915	7,744	4.6	142,867	8,106	6.7	113,189	8,044	7.1	<0.001
30–34	204,210	13,157	6.4	202,138	18,144	9.0	169,532	18,485	10.9	<0.001
35–39	65,070	5,118	7.9	66,822	6,827	10.2	59,487	7,356	12.4	<0.001
40–44	8,202	704	8.6	8,743	926	10.5	8,769	1,095	12.5	<0.001
≥ 45	561	15	2.7	570	28	4.9	525	30	5.7	<0.001
<30	201,117	8,497	4.2	171,474	9,029	5.3	139,061	8,992	6.5	<0.001
≥ 30	278,043	18,994	6.8	278,273	25,925	9.3	238,313	26,966	11.3	<0.001

ORIGINAL ARTICLE

A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes

Mild GDM: abnormal result on 100-g OGTT but FPG < 95 mg/dL

Table 2. Primary Perinatal Outcome.*

Outcome Variable	Treatment Group (N=485)	Control Group (N=473)	Relative Risk (97% CI)	P Value
Gestational age at birth — wk	39.0±1.8	38.9±1.8		0.87
Composite end point — no./total no. (%)†	149/460 (32.4)	163/440 (37.0)	0.87 (0.72–1.07)	0.14
Hypoglycemia‡	62/381 (16.3)	55/357 (15.4)	1.06 (0.73–1.53)	0.75
Hyperbilirubinemia‡	43/450 (9.6)	54/418 (12.9)	0.74 (0.49–1.12)	0.12
Elevated cord-blood C-peptide level‡	75/423 (17.7)	92/403 (22.8)	0.78 (0.57–1.05)	0.07
Stillbirth or neonatal death	0	0		
Birth trauma§	3/476 (0.6)	6/455 (1.3)	0.48 (0.10–2.20)	0.33

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

Table 4. Maternal Outcomes.*

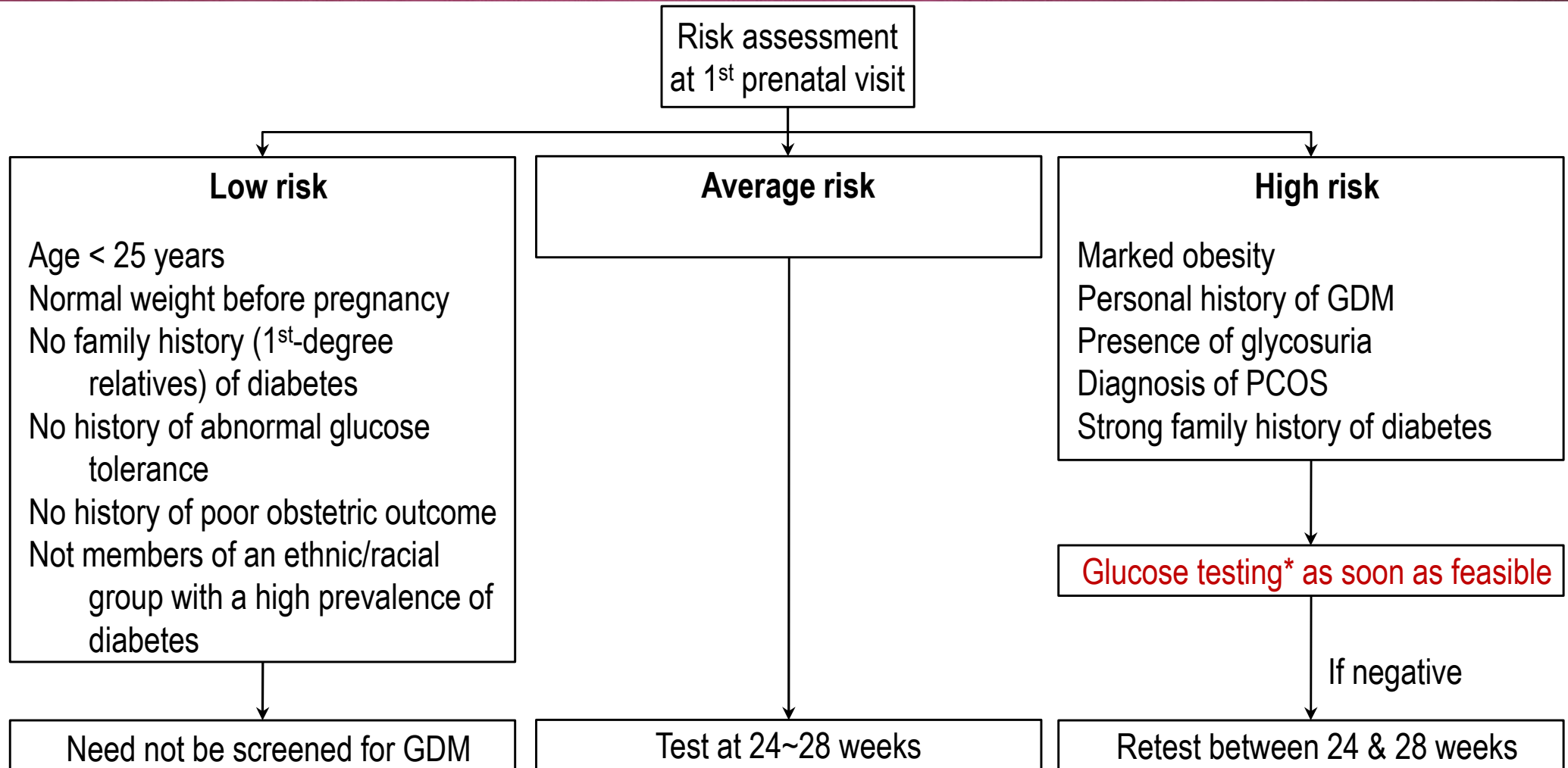
Outcome Variable	Treatment Group (N = 476)	Control Group (N = 455)	Relative Risk (97% CI)	P Value
Induction of labor — no. (%)	130 (27.3)	122 (26.8)	1.02 (0.81–1.29)	0.86
Cesarean delivery — no. (%)	128 (26.9)	154 (33.8)	0.79 (0.64–0.99)	0.02
Shoulder dystocia — no. (%)	7 (1.5)	18 (4.0)	0.37 (0.14–0.97)	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

GDM screening: 문제점

- 선별검사와 진단기준에 절대적인 기준이 없다.
 - **Universal vs. selective screening**
 - 선별검사 시기는?
 - 적절한 검사방법과 **cutoff value**?

GDM screening

ADA. Clinical Recommendation. 2010



Standard diagnostic test; FPG ≥ 126 mg/dL, casual glucose ≥ 200 mg/dL

In the absence of unequivocal hyperglycemia, the diagnosis must be confirmed on a subsequent day.

***Confirmation of the diagnosis precludes the need for any glucose challenge.**

GDM screening

Two-step approach

50-g glucose load

1-h

140 mg/dL



identify ~80% of women
with GDM (130 mg/dL, ~90%)

100-g glucose load

Fasting

95 mg/dL

1-h

180 mg/dL

2-h

155 mg/dL

3-h

140 mg/dL

75-g glucose load

Fasting

95 mg/dL

1-h

180 mg/dL

2-h

155 mg/dL

Two or more of concentrations; positive diagnosis

Should be done in the morning after an overnight fasting of between 8 & 14 hours and after at least

3 days of unrestricted diet and unlimited physical activity

Should remain seated throughout the test & should not smoke throughout the test

HAPO study

Objective: to clarify associations of levels of maternal glucose lower than those diagnostic of diabetes with perinatal outcome

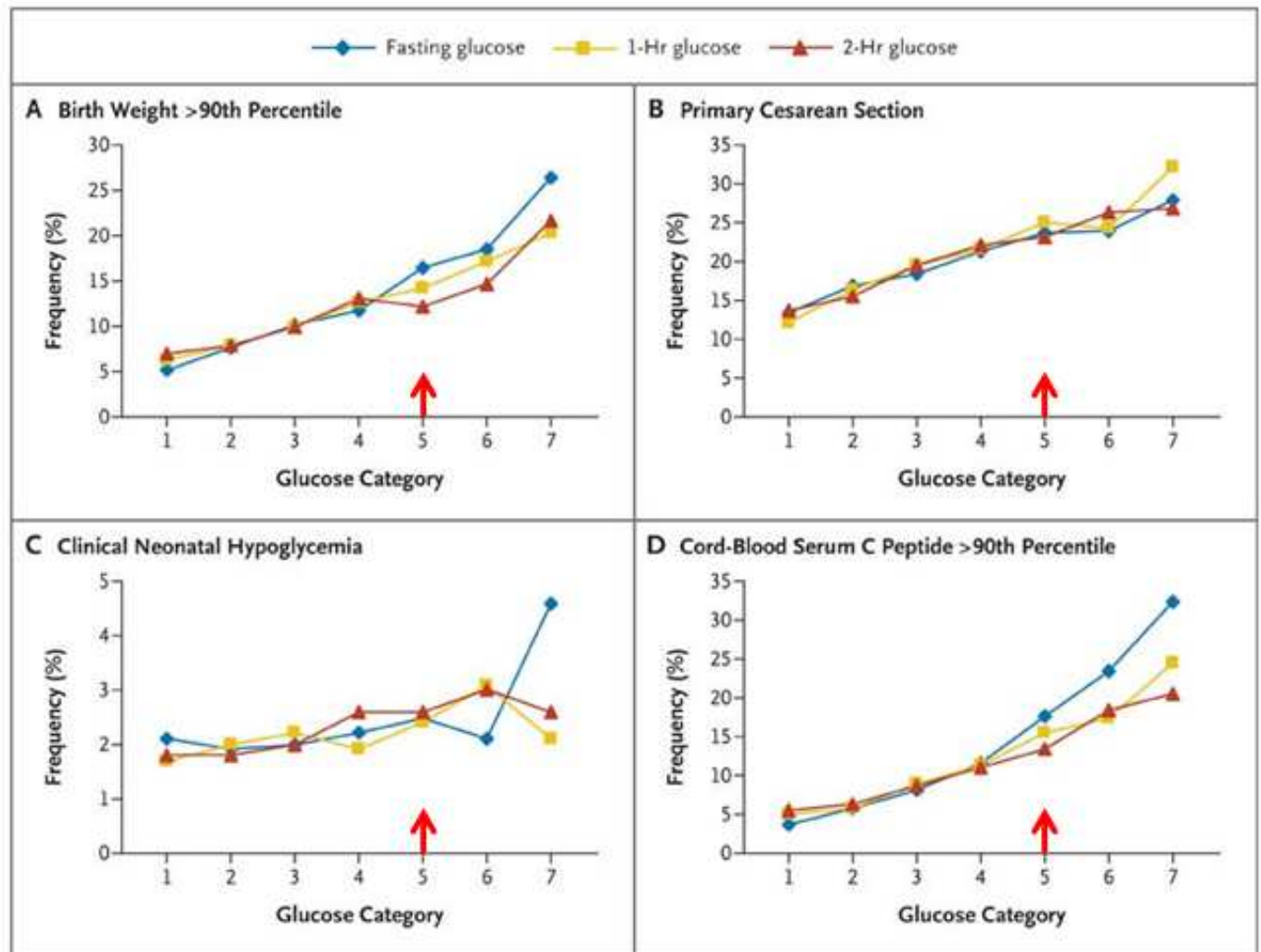
25,505 pregnant women

75-g OGTT at 24 to 32 weeks

FPG ≤ 105 mg/dL

2-hr PG ≤ 200 mg/dL

Continuous associations of maternal glucose levels below those diagnostic of diabetes with increased with birth weight & cord-blood c-peptide level
(No obvious threshold)



Threshold values for diagnosis of GDM or overt diabetes during pregnancy

To diagnose GDM & cumulative proportion of HAPO cohort equaling or exceeding those thresholds

Glucose measure	Glucose concentration threshold (mg/dL)*	Above threshold (Cumulative %)
FPG	92	8.3
1-h PG	180	14.0
2-h PG	153	16.1 [†] (+1.7)

*One of more of these values from 75-g OGTT must be equaled or exceeded for the diagnosis of GDM.

Reference: mean values for FPG, 1-h, & 2-h OGTT plasma glucose concentration (81, 134, 111 mg/dL)

Predefined value for the OR at the threshold relative to the mean should be **1.75**.

Diagnosis of “overt diabetes” during pregnancy

When - *On the initial visit for prenatal care*

Who - Performing in all vs. only high risk women

- On the basis of the background frequency of abnormal glucose metabolism
& on local circumstances

- Universal testing early: clinical value (?) or cost-effective (?)

Diagnosis of “overt diabetes” during pregnancy

How

To diagnose overt diabetes in pregnancy

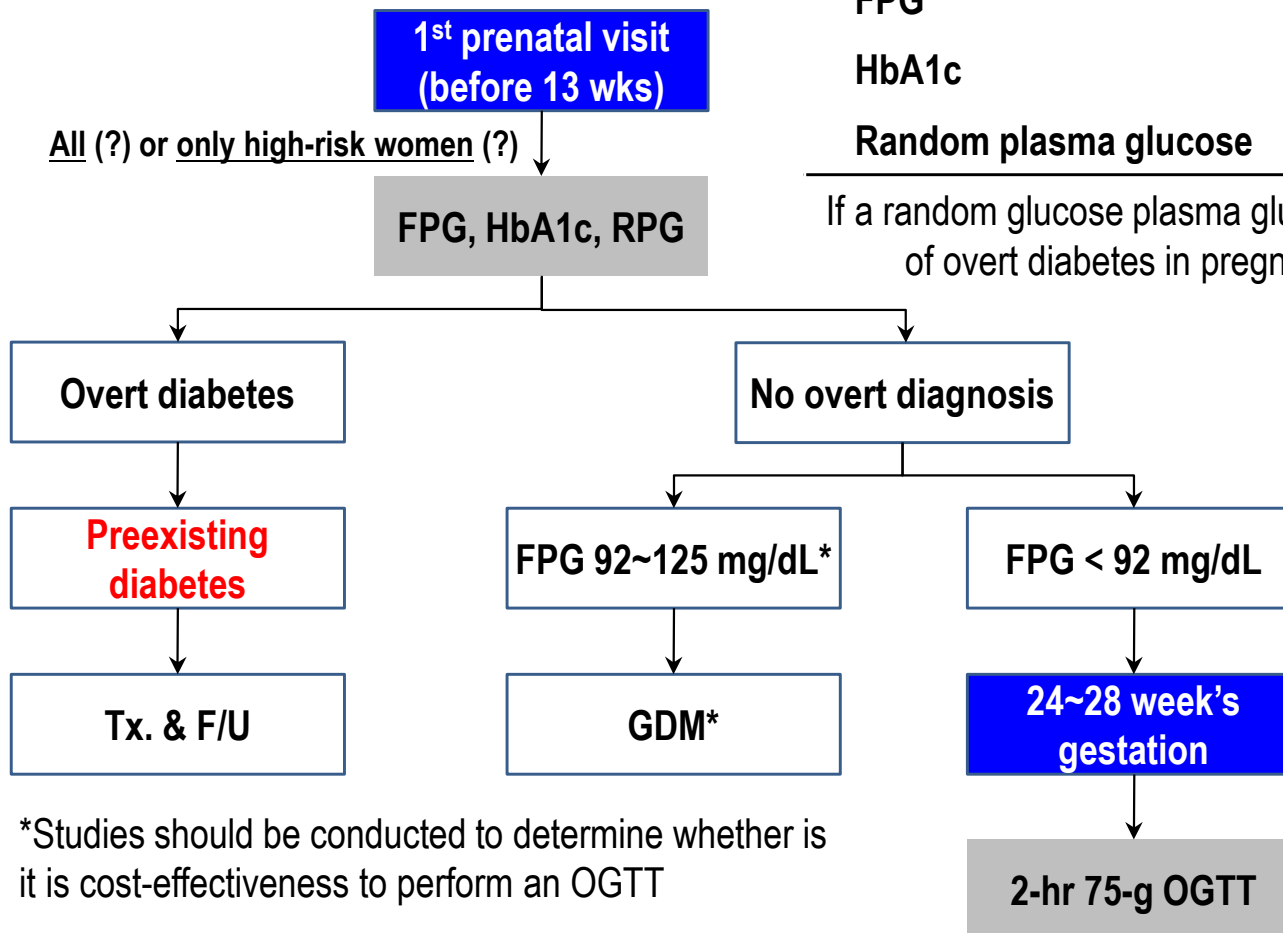
Measure of glycemia	Consensus threshold
FPG	≥ 126 mg/dL
HbA1c	$\geq 6.5\%$ (standardized methods)
Random plasma glucose	≥ 200 mg/dL + confirmation*

*If a random glucose plasma glucose is the initial measure, the tentative diagnosis of overt diabetes in pregnancy should be confirmed by FPG or HbA1c.

A little evidences whether there is benefit of generalized testing to diagnose & treat GDM before the usual window of 24~28 weeks' gestation

⇒ IADPSG Consensus panel does not recommend routinely performing OGTTs before 24~28 weeks' gestation

Strategy for the detection of hyperglycemic disorders in pregnancy



To diagnose overt diabetes in pregnancy

Measure of glycemia	Consensus threshold
FPG	≥ 126 mg/dL
HbA1c	≥ 6.5% (standardized methods)
Random plasma glucose	≥ 200 mg/dL + confirmation*

If a random glucose plasma glucose is the initial measure, the tentative diagnosis of overt diabetes in pregnancy should be confirmed by FPG or HbA1c.

To diagnose GDM using 75-g OGTT

Glucose measure	Threshold
FPG	92 mg/dL
1-h PG	180 mg/dL
2-h PG	153 mg/dL

Overt diabetes: FPG ≥ 126 mg/dL

GDM: one of more values equals or exceed threshold

Normal: all values on OGTT less than threshold

IADPSG 권고안의 문제점

- 환자 수 증가 (2-3배)
- **Cost-effectiveness**
- **Mild GDM 환자들은: clinical relevance... T2DM risk post partum...**

Different criteria for GDM

1st prenatal visit (before 13 weeks of gestation)

Endocrine Soc.

FPG (mg/dL)	92~125
RPG (mg/dL)	-
HbA1c (%)	-

24~28 weeks

WHO

Endocrine Soc.

ADA

ADA

Glucose challenge

50-g OGTT

1-hr (mg/dL)

≥ 140

Glucose challenge

75-g OGTT

75-g OGTT

100-g OGTT

75-g OGTT

Fasting (mg/dL)

92~125

92~125

≥ 95

≥ 92

1-hr (mg/dL)

≥ 180

≥ 180

≥ 180

≥ 180

2-hr (mg/dL)

153~199

153~199

≥ 155

≥ 153

3-hr (mg/dL)

≥ 140

No. of abnormal values

≥ 1

≥ 1

≥ 2

≥ 1

우리나라 임신부에게서 OGTT 인정기준

(고시 제2007-46호, 2007.6.1. 시행)

임산부에게 실시한 OGTT는 임신성당뇨병의 고위험군의 경우(소변검사상 당 검출, 4 kg이상의 거대아 분만력, 선천성 기형아 출산력, 당뇨의 가족력, 원인불명의 자궁내 태아사망의 분만력, 비만, 30세 이상의 산모 등)와 당뇨 기왕력이 있거나 의심되는 임신부에게 인정함을 원칙으로 하며, 100 g OGTT는 50 g OGTT 결과 140 mg/dL 이상인 경우 인정함.

우리나라 임신부에게서 OGTT 인정기준

(고시 제2015-217호, 2015.12.15. 시행)

- “산전진찰”에 50-g OGTT 포함

임신 24~28주 사이에 1회만 인정. 부하검사 시 사용한 약제 별도 인정.

- 100-g OGTT

50-g OGTT에서 140 mg/dL (고위험군 130 mg/dL) 이상인 경우 인정
산부인과에서 태아 모니터링 관리할 경우 관리료 추가

Preconception counseling in women with preexisting diabetes

- Strict glycemic control prior to conception: HbA1c < 6.5 (7.0)%
- Planned pregnancy
- HbA1c, TSH, Cr., urinary albumin to creatinine ratio, medication review, ophthalmologic exam
- Insulin 맞는 환자라면, MDI 또는 pump 고려
- Daily folic acid 5 mg to reduce the risk of neural tube defects

Preconception counseling in women with preexisting diabetes

- Detailed ocular assessment (qualified eye care professional)
 - If retinopathy (+) - 악화 가능성 설명하고, 미리 치료...
 - T/M마다 f/u, 분만 3개월 후 f/u
- BP control 110~129/65~79 mmHg
 - D/C RAS blocker d/t fetal damage
 - Chronic diuretics use: not recommended (restricted maternal plasma volume)
 - Methyldopa, labetalol, *diltiazem*, clonidine, prazosin
- D/C Statin, fenofibrate, niacin

Glycemic target in pregnancy

Premeal, bedtime	≤ 95 mg/dL	≤ 105 mg/dL*
1-hr postprandial	≤ 140 mg/dL	≤ 155 mg/dL*
2-hr postprandial	≤ 120 mg/dL	≤ 130 mg/dL*
HbA1c	$< 6.0\sim 6.5\%$ (6.0~7.0%)	

*If women cannot achieve these targets(left) without significant hypoglycemia, the American Diabetes Association(ADA) suggests less stringent targets based on clinical experience and individualization of care.

Management of diabetes in pregnancy

Glycemic monitoring in pregnancy

- HbA1c; monitored more frequently
- SMBG: testing before & either 1 or 2 hrs after the **start of each meal**, bedtime, during the night...

Management of diabetes in pregnancy

Management of GDM

- Target blood glucose levels as close to normal is possible
- Medical nutrition therapy
- Exercise for 30 minute or more
- Glucose monitoring
- If not controlled by MMT/exercise, insulin... glyburide, metformin

Management of diabetes in pregnancy

Insulin use in pregnancy

- 1st T/M 때는 total daily dose of insulin 감소.
- 2nd T/M 때는 다시 증가(d/t rapidly increasing insulin resistance)
- Basal insulin에 비해 **prandial insulin** 요구량이 많음.
- Approved for use in pregnancy (FDA category B)
 - Basal insulin; **Detemir**, NPH
 - Prandial insulin; **Lispro**, **aspart**, regular insulin

Treatment in pregnant women

- *Preferred agent: insulin*

- 1st T/M때는 인슐린요구량 감소, 2nd T/M때 다시 증가
- Basal insulin에 비해 prandial insulin 요구량이 많음.
- Approved for use in pregnancy (Category B)
 - Basal insulin; **Detemir**, NPH
 - Prandial insulin; **Lispro**, **aspart**, regular insulin

- Metformin

- Glyburide

Metformin in obese pregnant women without DM

Participants	450 pregnant women without DM who had BMI ≥ 35 kg/m ²
Intervention	Metformin 3.0 g/day
Comparator	Placebo
Period of treatment	12 to 18 wks of gestation to delivery
1° Outcome	Neonatal birth-weight
Results	
1° Outcome	No significant between-group difference
Maternal wt. gain	4.6 kg vs. 6.3 kg (P < 0.001)
Preeclampsia	3.0% vs. 11.3% (OR 0.24, 95% CI 0.10 to 0.61)
GDM/Adverse neonatal outcomes	No significant between-group difference

ORIGINAL ARTICLE

Metformin versus Insulin for the Treatment of Gestational Diabetes

- Equivalent pregnancy outcome, reduction in weight gain, less maternal hypoglycemia
- Need for supplemental insulin in metformin group: 46.3%



Original Research Article

The use of glyburide in the management of gestational diabetes mellitus: A meta-analysis

- Effective but...
- **Higher risk of neonatal hypoglycemia, fetal birth weight, & macrosomia**

FPG < 110 mg/dL이고 임신 25주 이상 GDM 환자

Treatment of GDM in Korea

HIRA database between 2009 & 2011

Table 3. Glucose-lowering therapy during pregnancy in patients with gestational diabetes mellitus (GDM) between 2009 and 2011.

	2009		2010		2011	
	n	(%)	n	(%)	n	(%)
Medical nutrition therapy only	26,154	(95.14)	33,686	(96.37)	34,495	(95.93)
Insulin only	1,317	(4.79)	1,250	(3.58)	1,441	(4.01)
OAD only	9	(0.03)	8	(0.02)	11	(0.03)
Insulin + OAD	11	(0.04)	10	(0.03)	11	(0.03)
Insulin	1,328	(4.83)	1,260	(3.60)	1,452	(4.04)
Sulfonylurea	3	(0.01)	4	(0.01)	7	(0.02)
Meglitinide	-	(0.00)	-	(0.00)	-	(0.00)
Metformin	18	(0.07)	15	(0.04)	17	(0.04)
Thiazolidinediones	-	(0.00)	1	(0.00)	-	(0.00)
DPP-4 inhibitor	1	(0.00)	1	(0.00)	-	(0.00)
α -glucosidase inhibitor	1	(0.00)	1	(0.00)	-	(0.00)

Case 1 (32/F, 1st IUP 26 wks, 65 kg)

	0 hr	1 hr	2 hr	3 hr
50-OGTT (mg/dL)	-	158	-	-
100-OGTT (mg/dL)	85	185	165	130
HbA1c (%)	5.8%			

SMBG (mg/dL)	Fasting	Post-breakfast	Post-lunch	Post-dinner
1 st	88	125	150	145
2 nd	85	115	162	152
3 rd	91	121	148	146

Humalog 8 U Humalog 8 U

SMBG (mg/dL)	Fasting	Post-breakfast	Post-lunch	Post-dinner
	82~92	105~115	110~125	112~120

Case 2 (38/F, 2nd IUP 28 wks, 80 kg)

	0 hr	1 hr	2 hr	3 hr
50-OGTT (mg/dL)	-	169	-	-
100-OGTT (mg/dL)	115	205	228	178
HbA1c (%)	6.8%			

SMBG (mg/dL)	Fasting	Post-breakfast	Post-lunch	Post-dinner
1 st	121	151	168	172
2 nd	119	155	182	182
3 rd	123	157	159	188

H-Mix₅₀ 12 U H-Mix₅₀ 16 U H-Mix₅₀ 16 U

SMBG (mg/dL)	Fasting	Post-breakfast	Post-lunch	Post-dinner
	80~88	108~122	105~120	110~132

Case 2 (35/F, 2nd IUP 24 wks, 85 kg, twin)

	0 hr	1 hr	2 hr	3 hr
50-OGTT (mg/dL)	-	-	-	-
100-OGTT (mg/dL)	98	189	165	145
HbA1c (%)	6.5%			

SMBG (mg/dL)	Fasting	Post-breakfast	Post-lunch	Post-dinner
1 st	95	145	159	168
2 nd	105	151	202	192
3 rd	98	142	176	176

	H-Mix₅₀ 16 U	H-Mix₅₀ 20 U	H-Mix₅₀ 20 U
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SMBG (mg/dL)	Fasting	Post-breakfast	Post-lunch	Post-dinner
	75~85	135~148	140~162	150~160

	Detemir 10 U	Humalog 12 U	Humalog 18 U	Humalog 18 U
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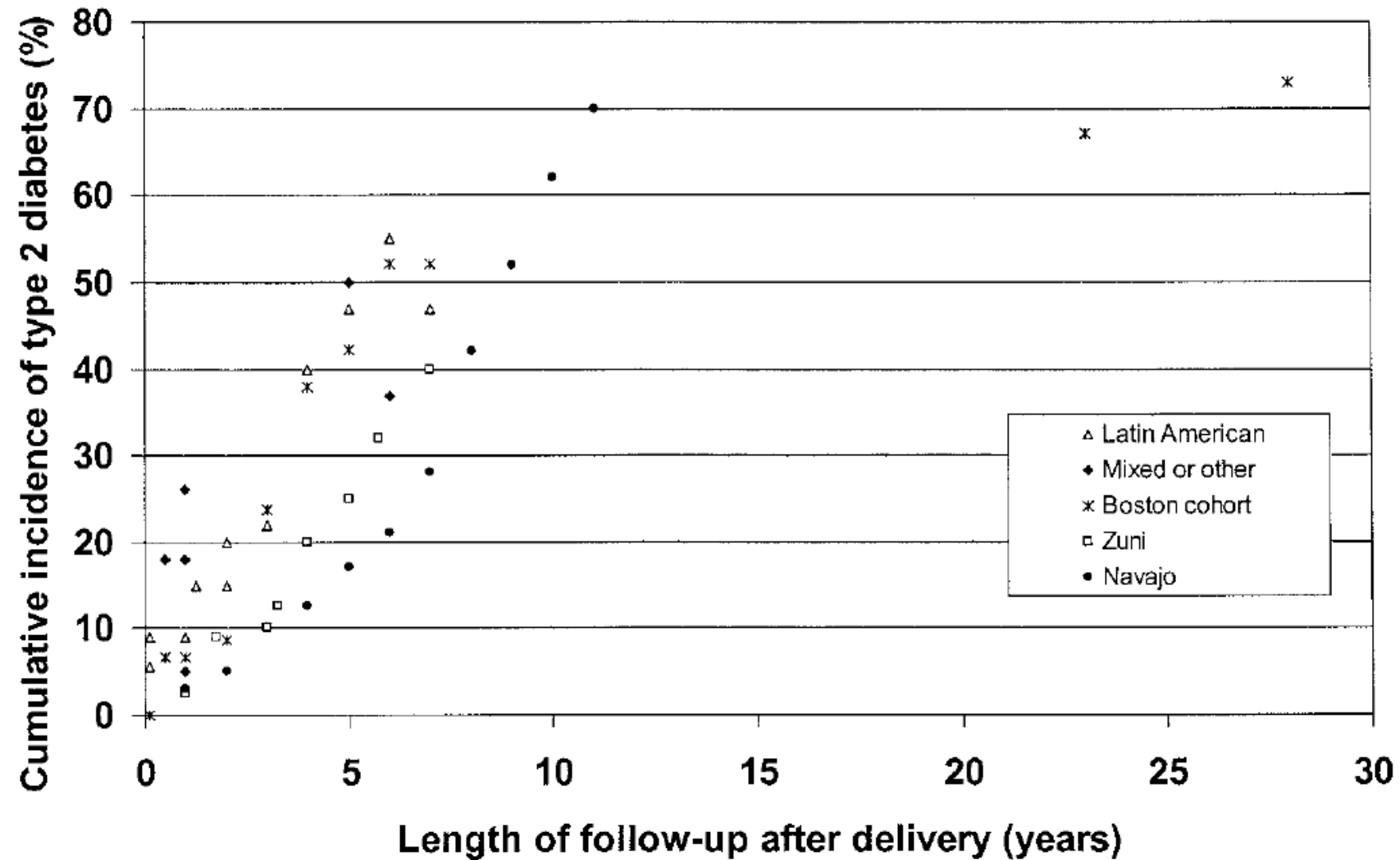
speaker's own contribution

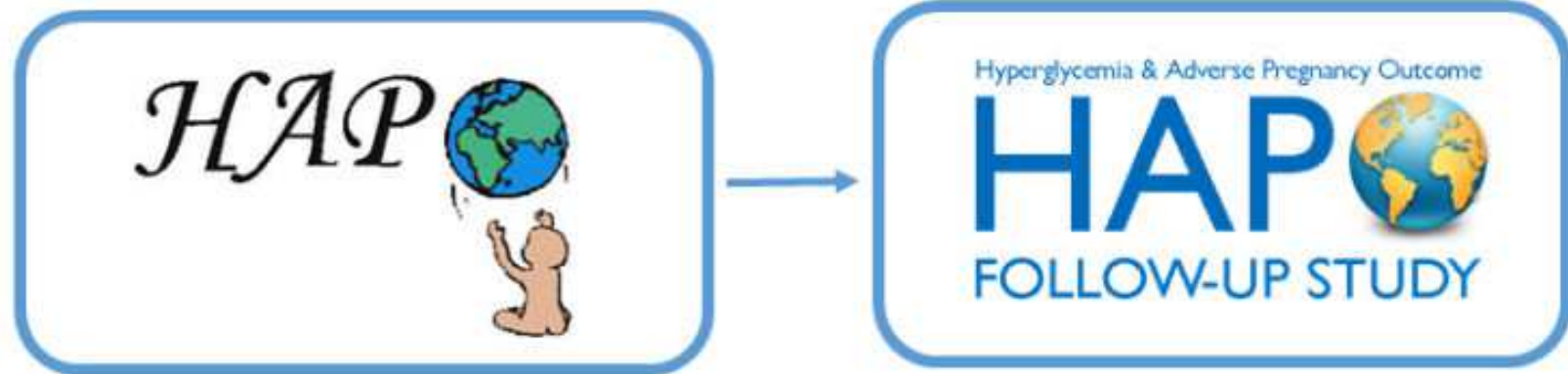
Postpartum management

In GDM: 분만 직후 **medication** 중단

In overt DM: 분만 직후 **insulin resistance** 급격히 감소...

GDM & incidence of T2DM





HAPO Follow-Up Study

Primary Hypothesis

Hyperglycemia in pregnancy, less severe than overt DM, is independently associated with increased risk of adverse childhood and maternal outcomes 8-12 years later.

Outcomes of the children according to the presence of GDM in their mothers

	No GDM	GDM
Proportion of overweight or obese children (%)	28.6	39.5
Proportion of obese children (%)	9.9	19.1

Outcomes of the mothers according to the presence of GDM during pregnancy

	No GDM	GDM
Prevalence of diabetes in HAPO FUS (%)	1.6	10.7
Prevalence of IFG in HAPO FUS (%)	9.7	30.8
Prevalence of IGT in HAPO FUS (%)	11.8	28.7
Any of the three (%)*	20.0	52.2

*Dose-response with 16.1% at OGTT value ≤ 74 mg/dL to 53.3% for ≥ 92 mg/dL

- Likelihood of having hypertension at F/U was not influenced by the previous GDM
- LDL-C, TG levels influenced by GDM

GDM: Postpartum monitoring

- FPG or fasting SMBG for 24~72 hrs after delivery
- **75-g OGTT 6~12 wks after delivery**
- Periodic screening periodically or before future pregnancy

Time	Test	Purpose
Post-delivery (1–3 days)	Fasting or random plasma glucose	Detect persistent, overt diabetes
Early postpartum (6-12 wk)	75-g 2-h OGTT	Postpartum classification of glucose metabolism
1 year postpartum	75-g 2-h OGTT	Assess glucose metabolism
Annually	Fasting plasma glucose	Assess glucose metabolism
Tri-annually	75-g 2-h OGTT	Assess glucose metabolism
Prepregnancy	75-g 2-h OGTT	Classify glucose metabolism

- Counseling on lifestyle measure, the need for future pregnancies to be planned, & the need for regular diabetes screening

Summary

- 당뇨병 여성은 계획 임신
- 당뇨병 병력이 없는 여성이 임신한 경우 적극적 **screening**
- 당뇨병 있다면 혈당은 거의 정상으로 유지
- 적절한 식사조절이 가장 중요
- 약물 치료 때는 **lispro or aspart/detemir** 부터 고려(**Humalog Mix**도 대안)
- **GDM** 병력을 가진 여성은 **long-term monitoring** 필요

경청해주셔서 감사합니다.

Gestational weight gain

(Institute of medicine guideline)

임신 전 BMI category	BMI (kg/m ²)	Recommended total weight gain (kg)	Recommended mean weight gain (kg/wk): 2 or 3 T/M
Underweight	< 18.5	12.5~18.0	0.51 (0.44~0.58)
Normal	18.5~24.9	11.5~16.0	0.42 (0.35~0.50)
Overweight	25.0~29.9	7.0~11.5	0.28 (0.23~0.33)
Obese	≥ 30.0	5.0~9.0	0.22 (0.17~0.27)