임신성 당뇨병의 관리

김 성 훈

관동의대 제일병원 내과

내 용

- 임신성 당뇨병의 정의와 임상적 의미
- 선별검사와 진단
- 발병원인
- 임신 중 관리
- 분만 후 관리와 추적 관찰

증 례

- 임신 28주의 32세 여성
- 임신 27주에 50g OCT:1시간 혈당이 174 mg/dL
- 100g OGTT: fasting-97 mg/dL, 1 hour-189 mg/dL, 2 hour-166mg/dL, 3 hour-140mg/dL
- 신장 164cm, 체중은 75kg (임신전 68kg)
- 혈압 110/70mmHg, 신체 검사, 소변검사나 다른 검사 소견은 정상

임신성 당뇨병의 정의

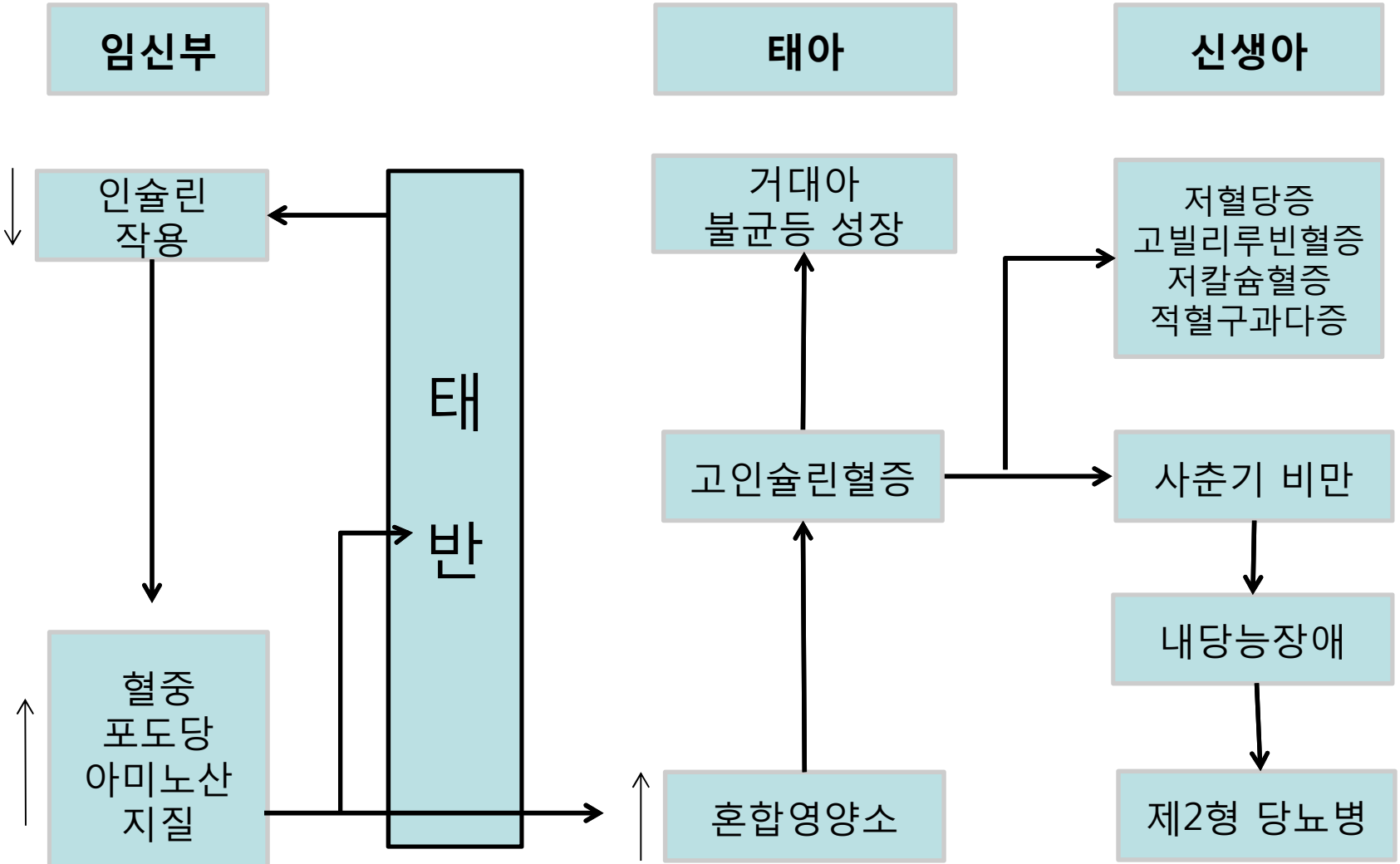
• Glucose intolerance of variable severity, with onset or first recognition during pregnancy

- Increasing prevalence of obesity and diabetes
  - ↑ T2DM in women of childbearing age
  - ↑ pregnant women with undiagnosed T2DM

- Diabetes at initial prenatal visit, using standard criteria
  → overt, not gestational, diabetes (IADPSG 2010)

- In Korea: 2-5% of all pregnancies

Pedersen-Freinkel 가설



임신성 당뇨병의 임상적 의미

- Perinatal complications (fetal or neonatal)

  - excessive fetal growth (macrosomia)
  - shoulder dystocia, birth injury (bone fracture and nerve palsies)
  - hypoglycemia, hyperbilirubinemia, hypocalcemia, erythremia, poor feeding
  - high risk of developing glucose intolerance and obesity in the offspring at a young age

- Maternal complications

  - morbidity from operative delivery
  - maternal birth trauma
  - preterm labor
  - preeclampsia
  - a lifetime risk of diabetes mellitus

Frequency of perinatal complications in women with mild to moderate GDM without treatment

Table 2 | Perinatal outcomes in the HAPO cohort*

Outcome	Frequency in pregnancies affected by GDM (%)	Frequency in pregnancies not affected by GDM (%)	Frequency difference (%)
Pre-eclampsia	9.1	4.5	4.6
Delivery at <37 weeks	9.4	6.4	3.0
Primary caesarean delivery	24.4	16.8	7.6
Shoulder dystocia or birth injury	1.8	1.3	0.5
Intensive neonatal care	9.1	7.8	1.3
Clinical neonatal hypoglycaemia	2.7	1.9	0.8
Neonatal hyperbilirubinaemia	10.0	8.0	2.0
Birthweight >90th percentile	16.2	8.3	7.9
Cord C-peptide levels >90th percentile	17.5	6.7	10.8
Percent body fat >90th percentile	16.6	8.5	8.1

*GDM diagnosed according to IADPSG criteria (Table 1). Abbreviations: GDM, gestational diabetes mellitus; HAPO, Hyperglycemia and Adverse Pregnancy Outcomes; IADPSG, International Association for Diabetes and Pregnancy Study Groups. Permission obtained from the American Diabetes Association © Metzger, B. E. *et al. Diabetes Care* **33**, 676–682 (2010).[4]

Buchanan TA et al. Nat. Rev Endocrinol 8: 639, 2012

선별검사와 진단검사

TABLE 2. SERUM OR PLASMA GLUCOSE SCREENING FOR GESTATIONAL DIABETES MELLITUS WITH THE 50-g ORAL GLUCOSE-CHALLENGE TEST.*

SERUM GLUCOSE CUTOFF POINT†	PROPORTION OF WOMEN WITH POSITIVE TEST‡	SENSITIVITY FOR GESTATIONAL DIABETES MELLITUS‡
	percent	
≥140 mg/dl (7.8 mmol/liter)	14–18	~80
≥130 mg/dl (7.2 mmol/liter)	20–25	~90

*Recommendations are adapted from Metzger et al.[1] Serum or plasma glucose is measured one hour after the glucose challenge, which can be performed at any time of day, without regard to the time of the last meal. In women with very-high-risk clinical characteristics, diagnostic testing may be performed without prior glucose screening.[1]

†Venous serum or plasma glucose concentration is measured by methods with high precision and appropriate quality control.

‡The percentage may vary according to race or ethnic group and the glucose-tolerance-test criteria used for diagnosis.

Table 2—*Diagnosis of GDM by an oral glucose tolerance test*

	Oral glucose load*			
	100-g glucose†		75-g glucose†	
Fasting‡	95 mg/dl	5.3 mmol/l	95 mg/dl	5.3 mmol/l
1-h‡	180 mg/dl	10.0 mmol/l	180 mg/dl	10.0 mmol/l
2-h‡	155 mg/dl	8.6 mmol/l	155 mg/dl	8.6 mmol/l
3-h‡	140 mg/dl	7.8 mmol/l	—	—

Data are from Metzger et al. (9). *The test should be performed in the morning after an overnight fast of at least 8 h but not more than 14 h and after at least 3 days of unrestricted diet (≥150 g carbohydrate/day) and physical activity. The subject should remain seated and should not smoke throughout the test. †Two or more of the venous plasma glucose concentrations indicated below must be met or exceeded for a positive diagnosis. ‡The cutoff values are those proposed by Carpenter and Coustan (10) for extrapolation of the whole blood glucose values found by O'Sullivan and Mahan (11) to plasma glucose concentrations.

Table 6—*Screening for and diagnosis of GDM*

Perform a 75-g OGTT, with plasma glucose measurement fasting and at 1 and 2 h, at 24–28 weeks' gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are exceeded:

- Fasting ≥92 mg/dL (5.1 mmol/L)
- 1 h ≥180 mg/dL (10.0 mmol/L)
- 2 h ≥153 mg/dL (8.5 mmol/L)

ADA: Standards of Medical Care in Diabetes—2013. Diabetes Care 36:S11-S66

임신성 당뇨병의 진단기준

I. 선별검사

1. 모든 산모는 첫 산전 방문 시에 공복혈당, 무작위 혈당, 혹은 당화혈색소 측정을 통해 기왕의 당뇨병 여부에 대한 검사를 하는 것이 좋다. [E]
2. 이전에 당뇨병이나 임신성 당뇨병으로 진단받지 않은 산모는 임신 24–28주에 2시간 75 g 경구당부하검사를 시행할 수 있다 (1단계 접근법, one step approach). [E]
3. 기존의 2단계 접근법 (two step approach)를 이용할 경우는 50 g 당부하 1시간 후 혈당 140 mg/dL 이상 (고위험 산모의 경우, 130 mg/dL)이면 선별검사 양성으로 판정하여 100 g 경구당부하검사 시행을 고려한다. [E]

당뇨병 진료지침 2011, 대한당뇨병학회

II. 진단기준

1. 첫 번째 산전 방문 검사 시 다음 중 하나 이상을 만족하면 기왕의 당뇨병이 있는 것으로 진단한다. [E]
   1-1. 공복 혈장 혈당 ≥ 126 mg/dL
   1-2. 무작위 혈장 혈당 ≥ 200 mg/dL
   1-3. 당화혈색소 ≥ 6.5%

2. 임신 24-28주 사이에 시행한 2시간 75 g 경구당부하검사 결과 다음 중 하나 이상을 만족하는 경우 임신성 당뇨병으로 진단할 수 있다. [E]
   2-1. 공복 혈장 혈당 ≥ 92 mg/dL
   2-2. 당부하 1시간 후 혈장 혈당 ≥ 180 mg/dL
   2-3. 당부하 2시간 후 혈장 혈당 ≥ 153 mg/dL

3. 기존의 2단계 접근법으로 100 g 경구당부하검사를 시행한 경우는 다음 기준 중 두 가지 이상을 만족하는 경우 임신성 당뇨병으로 진단한다. [E]
   3-1. 공복 혈장 혈당 ≥ 95 mg/dL
   3-2. 당부하 1시간 후 혈장 혈당 ≥ 180 mg/dL
   3-3. 당부하 2시간 후 혈장 혈당 ≥ 155 mg/dL
   3-4. 당부하 3시간 후 혈장 혈당 ≥ 140 mg/dL

발병 원인

- Autoimmune destruction of the pancreatic cells
- Monogenic diabetes
- Similarities to type 2 diabetes
  : β-cell defects and insulin resistance

Rationale for treatment of mild GDM

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*

- Conclusion

  Treatment of gestational diabetes reduces serious perinatal morbidity and may also improve the woman's health-related quality of life

NEJM 352:24, 2005

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes

Mark B. Landon, M.D., Catherine Y. Spong, M.D., Elizabeth Thom, Ph.D., Marshall W. Carpenter, M.D., Susan M. Ramin, M.D., Brian Casey, M.D., 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., and Garland B. Anderson, M.D., for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

CONCLUSIONS

Although treatment of mild gestational diabetes mellitus did not significantly reduce the frequency of a composite outcome that included stillbirth or perinatal death and several neonatal complications, it did reduce the risks of fetal overgrowth, shoulder dystocia, cesarean delivery, and hypertensive disorders. (ClinicalTrials.gov number, NCT00069576.)

NEJM 361:1339, 2009

임신 중 관리

- Goals of management
  - to prevent perinatal mortality and morbidity
  - to achieve and maintain normoglycemia

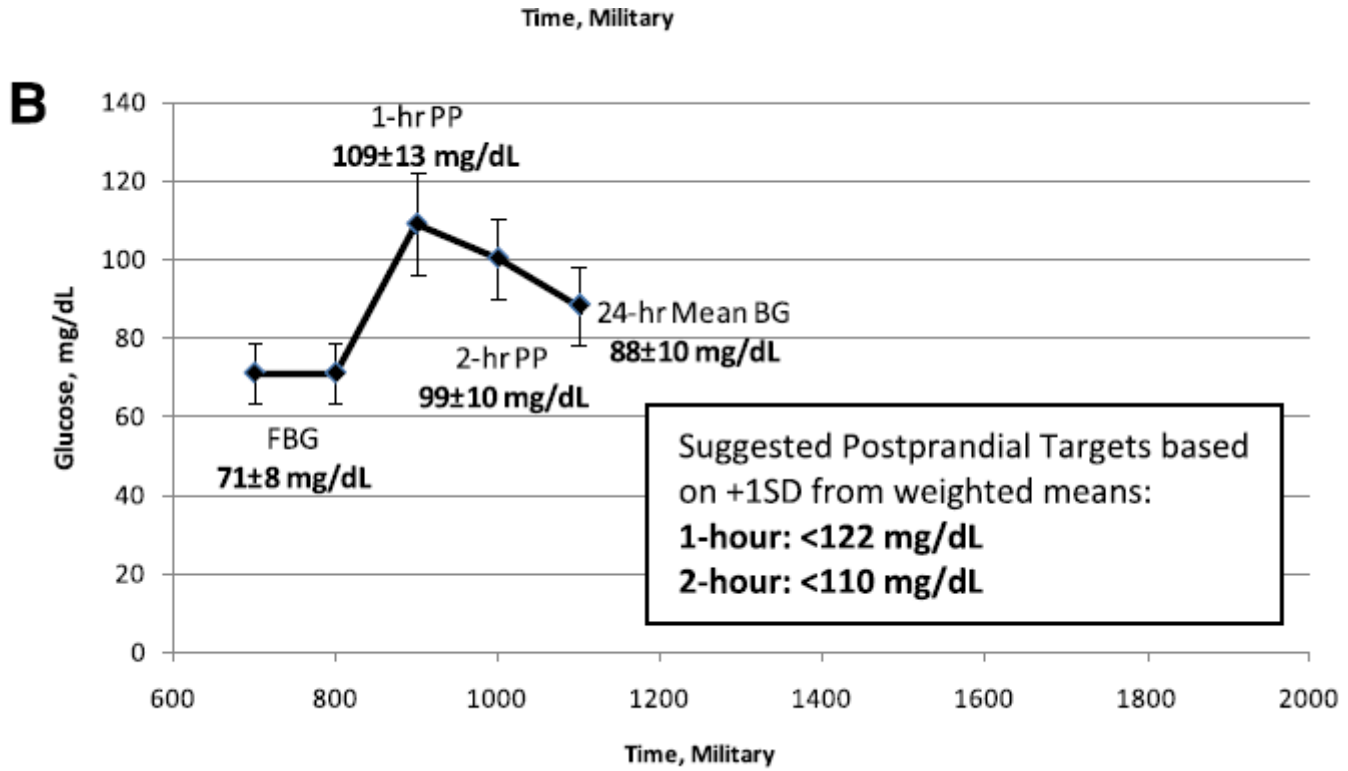
- Blood glucose goals (by ADA)

  Fasting whole blood glucose ≤ 95 mg/dL

  1-h postprandial whole blood glucose ≤ 140 mg/dL

  2-h postprandial whole blood glucose ≤ 120 mg/dL

Patterns of glycemia in normal pregnancy



B: *Mean pattern of glycemia across 12 studies (n = 168–255) during 33.8 ± 2.3 weeks' gestation (weighted average ± SD, values rounded to whole numbers for clinical use). Suggested 1- and 2-h PP targets are <122 and <110 mg/dL, respectively.*

Hernandez TL et al. Diabetes Care 2011;34:1660-68

임상영양치료

- MNT: the cornerstone of Tx for GDM

- Goals of MNT

  - provide the necessary nutrients for maternal/fetal health

  - to maintain normoglycemia

  - prevent ketosis

  - to allow for the appropriate weight gain

“Individualized MNT”

- Total calories: 25-32 kcal/BW (30-35 kcal/IBW)

  - A 30% of calorie restriction in obese women (BMI >30) (~25 kcal/kg actual weight per day)

  : reduce hyperglycemia and plasma TG and no increase in ketonuria

- Carbohydrate-restricted diet

  : 35-40% (by ADA), 50% in Korea (Park et al, 2001)

  reduce maternal blood glucose values and improve fetal outcome

- Carbohydrates with low GI

  - reduce postprandial hyperglycemia and to provide sufficient slow-release CHO to prevent hypoglycemia between meals

- Small frequent meals: 3 main meals and 2 to 3 snacks

Goals for weight gain (1)

Prepregnancy BMI	Total wt.gain (kg)	Rate of wt.gain(2&3Tri.)kg/wk
Underweight (<18.5)	12.5 - 18	0.51 (0.44-0.58)
Normal weight (18.5-24.9)	11.5 - 16	0.42 (0.35-0.50)
Overweight (25-29.9)	7 - 11.5	0.28 (0.23-0.33)
Obese (≥30)	5 - 9	0.22 (0.17-0.27)

** Calculations assume a 0.5–2 kg (1.1–4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997)*

Institute of Medicine, 2009

Goals for weight gain (2)

- Less weight gain is safe and has a beneficial effect on perinatal outcomes in obese women: a weight gain of 0-7 pounds was associated with the least macrosomia

Cheng YW et al. Gestational weight gain and gestational diabetes mellitus: perinatal outcomes. Obstet Gynecol 112:1015-1022, 2008

Low gestational weight gain improves infant and maternal pregnancy outcomes in overweight and obese Korean women with gestational diabetes mellitus

JEONG EUN PARK[1], SUNMIN PARK[2], JAMES W. DAILY[3], & SUNG-HOON KIM[1]

[1]*Division of Endocrinology & Metabolism, Department of Medicine, Cheil General Hospital & Women's Healthcare Center, Seoul, Korea,* [2]*Department of Food & Nutrition, Hoseo University, Asan, Korea, and* [3]*Daily manufacturing Inc., Rockwell, NC, USA*

(Received 25 July 2010; revised 19 October 2010; accepted 10 November 2010)

Abstract

Objective. The aim of the study was to retrospectively assess what was the optimal gestational weight gain to have better maternal and neonatal outcomes in overweight and obese Korean women with gestational diabetes mellitus (GDM) who maintained normoglycemia throughout pregnancy by dietary modification, exercise, and/or insulin treatment.

Study design. We performed a hospital-based study of 215 GDM women with prepregnancy BMI ≥ 25 kg/m^2. Body weight, glucose homeostasis, lipid profiles, insulin treatment, and maternal outcomes were collected as predictors of neonatal birth weight. We divided the subjects into three groups according to modified Institute of Medicine (IOM) guidelines for weight gain during pregnancy: inadequate ($n = 42$), normal ($n = 96$), and excessive ($n = 77$) groups.

Results. Excessive weight gain resulted in increased macrosomia, HbA_{1c} at delivery, and postprandial blood glucose levels, but fasting blood glucose levels were not significantly different among the groups. The inadequate weight gain group (2.4 kg weight gain during pregnancy) had better neonatal outcomes and better maternal glycemic control with fewer requiring insulin treatment.

Conclusion. Minimal weight gain, well below IOM recommendations, and tight control of blood glucose levels during pregnancy with proper medical management and dietary modification may eliminate most of the adverse pregnancy outcomes experienced by obese GDM Asian women.

Gynecol Endocrinol 2011: 27:775-81

운동요법

- Improve insulin sensitivity and reduce hyperglycemia

- Should not cause fetal distress, uterus contraction, or hypertension
  :upper body cardiovascular training

- Less than 30 minutes of low to moderate physical activity (walking and swimming)

검사 (surveillance)

- Maternal glycemia (daily SMBG)
  : self-monitoring of blood glucose (SMBG)- 4-7 times/day
  (before breakfast , 1-2hr after breakfast, lunch, and dinner)

- US measurement of fetal abdominal circumference
  : 2nd and early 3rd trimesters and repeated every 3-6 weeks

- Urine ketone
  : severe hyperglycemia,
  weight loss during treatment
  insufficient caloric or CHO intake (starvation ketosis)

- Glycosylated Hb or other circulating proteins

인슐린 치료

- When nutritional therapy fails to maintain glycemic goals or who show signs of excessive fetal growth
  - Two major approaches
    1. glycemia criteria
    2. fetal growth-based strategy (fetal AC)

- Human insulin (NPH and RI) and insulin analogues (lispro, aspart, premix insulin, and detemir)

- Insulin administration be individualized (ex, MDI and Insulin pump)

경구혈당강하제

- A randomized clinical trial in 404 GDM mothers
  (glyburide vs insulin)
  - mean blood glucose levels were similar in two groups
  - similar perinatal outcomes
  - glyburide does not appear to cross human placenta (4% ex vivo)
  - in the setting of GDM, glyburide and insulin are equally effective

Langer et al.NEJM 343:1134, 2000

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Metformin versus Insulin for the Treatment of Gestational Diabetes

Janet A. Rowan, M.B., Ch.B., William M. Hague, M.D., Wanzhen Gao, Ph.D., Malcolm R. Battin, M.B., Ch.B., and M. Peter Moore, M.B., Ch.B., for the MiG Trial Investigators*

CONCLUSIONS

In women with gestational diabetes mellitus, metformin (alone or with supplemental insulin) is not associated with increased perinatal complications as compared with insulin. The women preferred metformin to insulin treatment. (Australian New Zealand Clinical Trials Registry number, 12605000311651.)

Rowan JA et al.NEJM 358:2003, 2008

산과 관리

- Fetal surveillance
  - Fetal US screening for congenital anomalies (FPG >120 mg/dl or A1c ≥7%)
  - Fetal US to detect fetal macrosomia
  - fetal movement during the last 8-10 wks of preg
  - Optimal application of more intensive fetal monitoring: no data

- Maternal surveillance
  - Use of corticosteroids to enhance fetal lung maturity: intensified glucose monitoring
  - risk of hypertensive disorder↑: BP and urine protein

Summary of antepartum care

- Medical Nutritional therapy
- Regular exercise
- Maternal SMBG or fetal AC for intensified Tx
- Insulin remains the mainstay of Tx
- glyburide and metformin may be offered as an alternative

분만시 혈당 관리

- Most women with GDM will not require insulin during labor
- Continue measuring BG
- When induction is planned, insulin and breakfast should be omitted in the morning and iv fluids begun (5% dextrose in half-normal saline, 100 ml/h)
- If BG >120 mg/dl, short-acting insulin, 1U/h iv (adjust the dosage to maintain the BG 70-120 mg/dl)
- Insulin infusion discontinued immediately before delivery and, in most cases, will not need to be resumed postpartum

분만 후 합병증

- Recurrence of GDM
  : ~ 50% in Korean women
  (Kwak SH et al, Diabetes Care 31: 1867, 2008)

- Development of T2DM
  : 30-50% within 5-10 years

- A higher incidence of the metabolic syndrome

- Early atherosclerosis (endothelial dysfunction)
  : increased risk of chronic hypertension and CVD

분만 후 관리

- CVD risk factor assessment
- Breast feeding
- Contraception or pregnancy planning
- Diabetes prevention

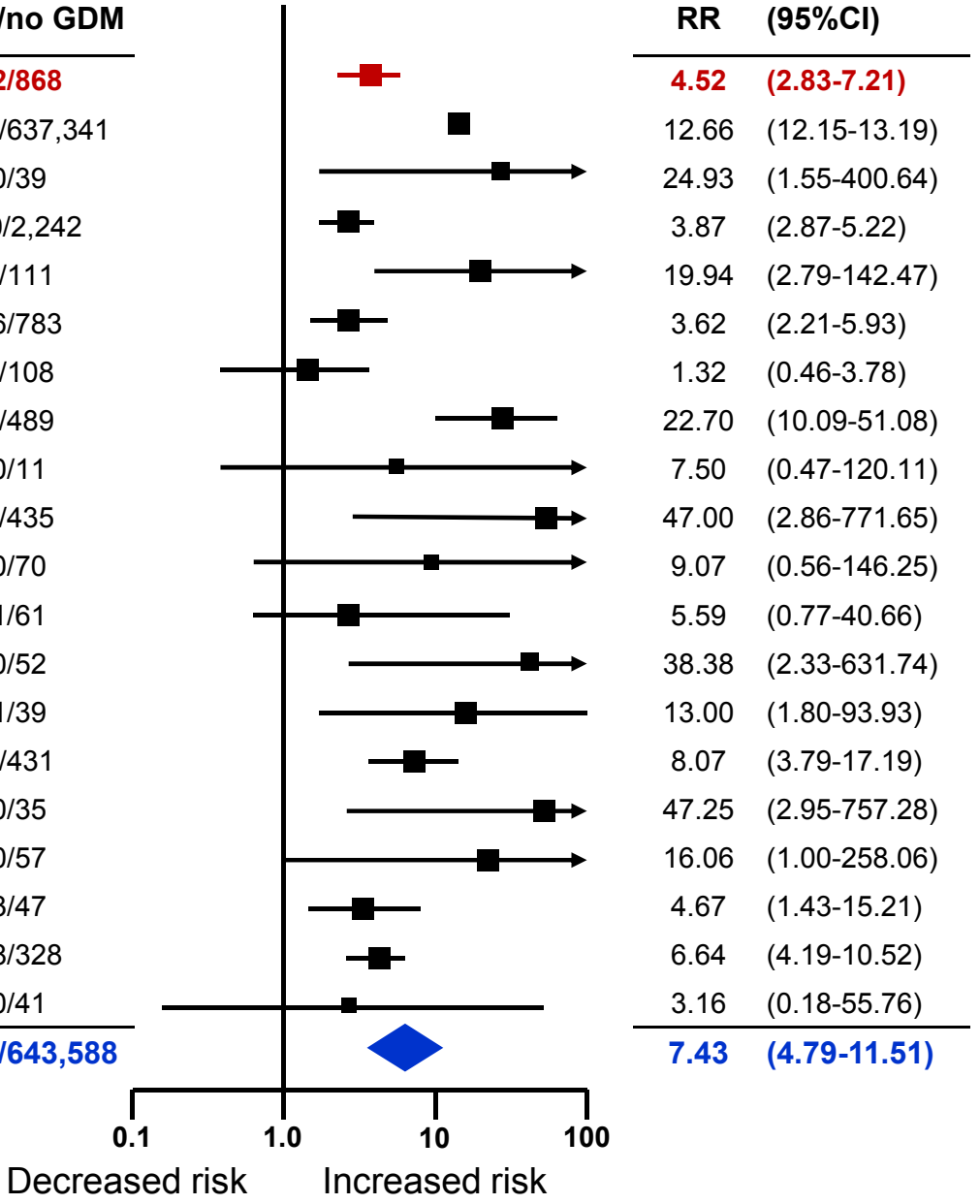
Mitigation of the risk of DM

- The first step is to decide what type of GDM the patient had

  :β-cell dysfunction related to islet autoimmunity or monogenic diabetes

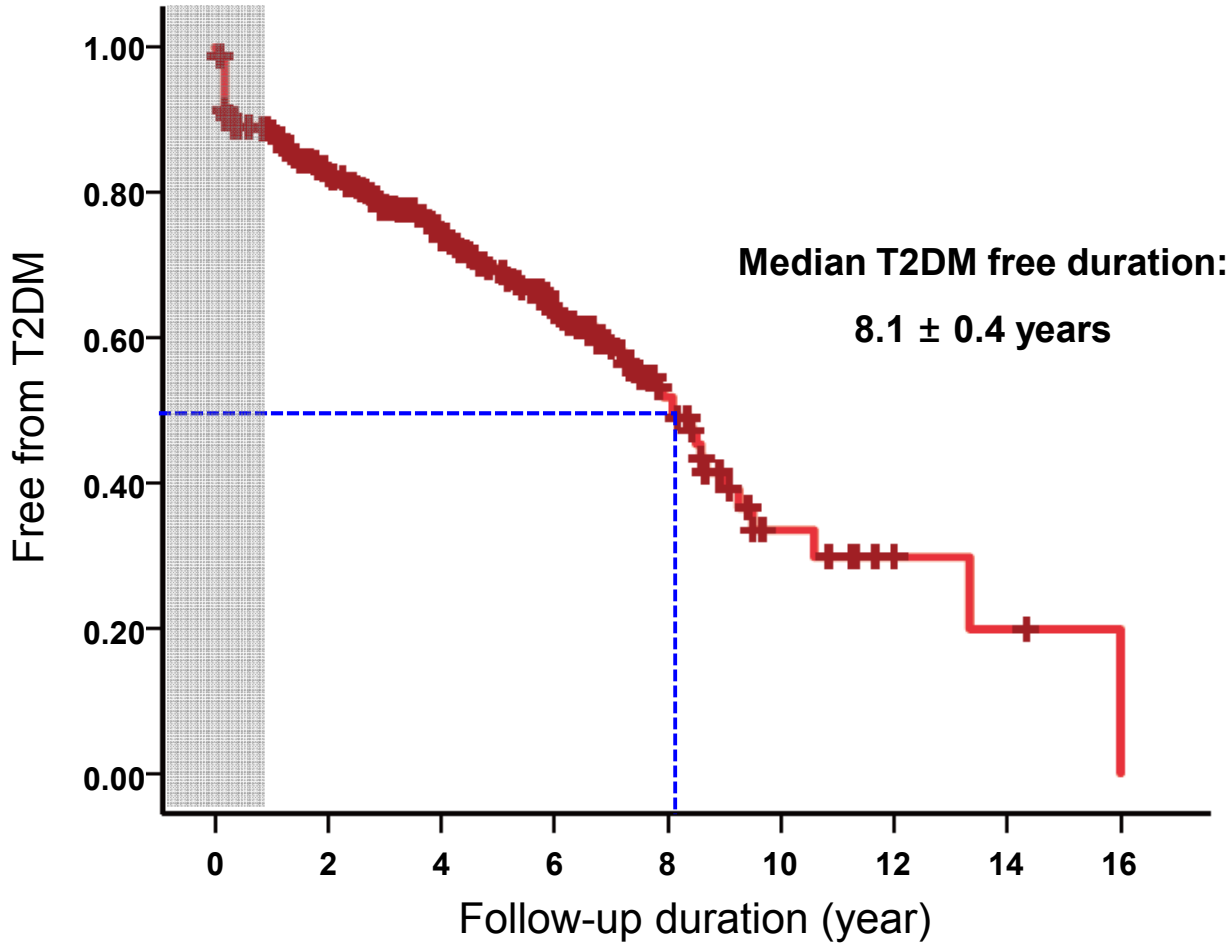
Risk of T2DM after GDM

Study	Year	Country	T2DM/GDM	T2DM/no GDM	RR	(95%CI)
Lee H et al	**1995-1997**	**Korea**	**71/620**	**22/868**	**4.52**	**(2.83-7.21)**
Feig et al	1995-2002	Canada	2,874/21,823	6,628/637,341	12.66	(12.15-13.19)
Madarasz et al	1995	Hungary	21/68	0/39	24.93	(1.55-400.64)
Gunderson et al	1985-2006	USA	43/166	150/2,242	3.87	(2.87-5.22)
Vambergue et al	1992	France	53/295	1/111	19.94	(2.79-142.47)
Lee A et al	1971-2003	Australia	405/5,470	16/783	3.62	(2.21-5.93)
Ferraz et al	2007	Brazil	6/70	7/108	1.32	(0.46-3.78)
Krishnaveni et al	1997-1998	India	13/35	8/489	22.70	(10.09-51.08)
Morimitsu et al	1999-2001	Brazil	7/23	0/11	7.50	(0.47-120.11)
Jarvela et al	1984-1994	Finland	23/435	0/435	47.00	(2.86-771.65)
Albareda et al	1966-1993	Spain	44/696	0/70	9.07	(0.56-146.25)
Aberg et al	1991-1999	Sweden	21/229	1/61	5.59	(0.77-40.66)
Linne et al	1964-1965	Sweden	10/28	0/52	38.38	(2.33-631.74)
Bian et al	1964-1965	China	15/45	1/39	13.00	(1.80-93.93)
Ko et al	1988-1995	China	105/801	7/431	8.07	(3.79-17.19)
Osei et al	1990-1991	USA	10/15	0/35	47.25	(2.95-757.28)
Damm et al	1978-1985	Denmark	33/241	0/57	16.06	(1.00-258.06)
Benjamin et al	1961-1988	USA	14/47	3/47	4.67	(1.43-15.21)
O'Sullivan et al	1962-1970	USA	224/615	18/328	6.64	(4.19-10.52)
Persson et al	1961-1984	Sweden	5/145	0/41	3.16	(0.18-55.76)
Total			**3,997/31,867**	**6,862/643,588**	**7.43**	**(4.79-11.51)**



Bellamy et al. Lancet 2009

Incidence of T2DM after GDM in Koreans



Risk factors for conversion from GDM to type 2 diabetes

- Fasting glucose value on OGTT
- Obesity precedes pregnancy
- Postpartum weight gain
- GDM diagnosed before the 24th week of pregnancy
- Relative insulinopenic response to oral glucose
- The requirement for insulin in pregnancy
- Family history of type 2 diabetes, esp on the maternal side
- Maternal age
- Parity
- Previous history of GDM

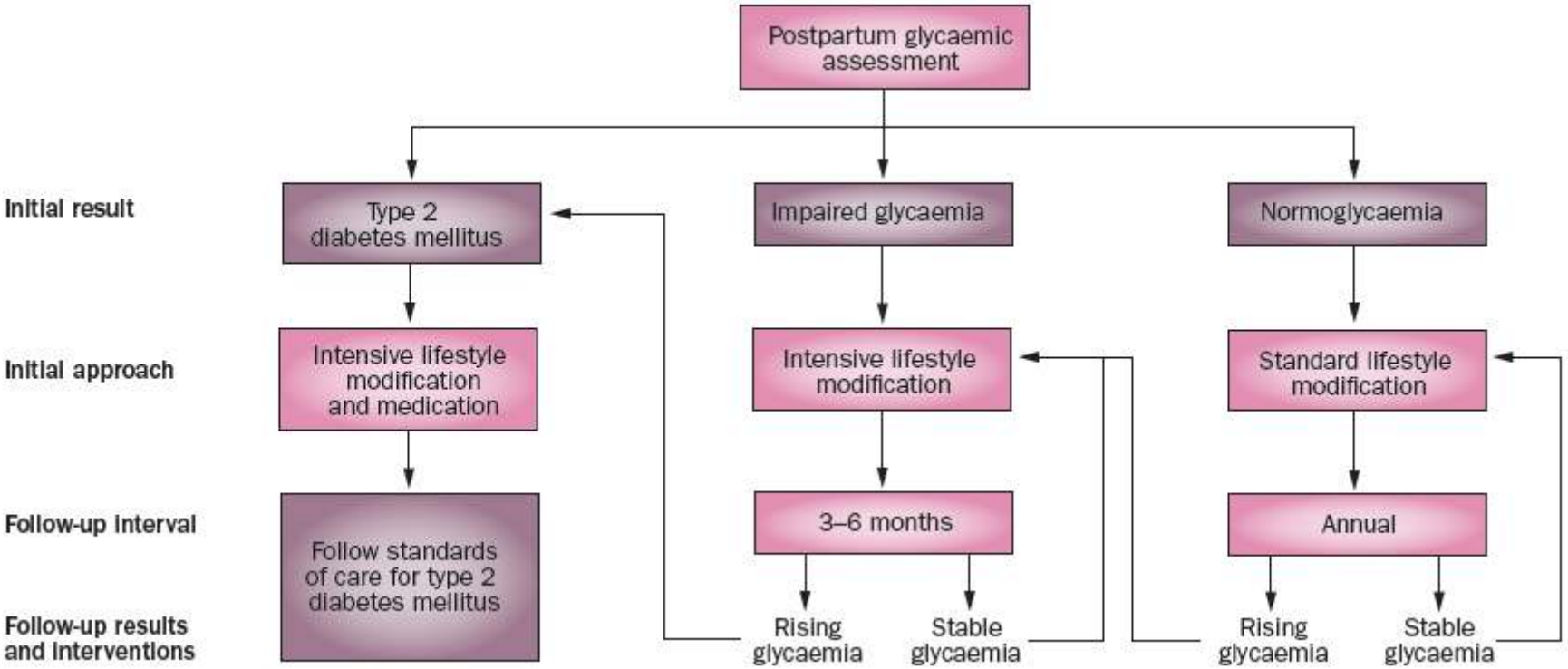
분만 후 혈당 검사

Table 2—*Metabolic assessments recommended after GDM*

Time	Test	Purpose
Post-delivery (1–3 days)	Fasting or random plasma glucose	Detect persistent, overt diabetes
Early postpartum (around the time of postpartum visit)	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

Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus, Diabetes Care 30 (Suppl.2), 2007

Management of women with prior GDM



Buchanan TA et al. Nat. Rev Endocrinol 8: 639, 2012

Prevention of T2DM in women with GDM

- In women with a history of GDM, Metformin and intensive lifestyle: ~50% reduction in the risk of diabetes

- Women with a history of GDM found to have prediabetes should receive lifestyle interventions or metformin to prevent diabetes

ADA: Standards of Medical Care in Diabetes—2013.
Diabetes Care 36:S11-S66

Future directions

- Risk and timeline for progression to diabetes

- Appropriate preventive strategies

  - Optimal timing and cost-effectiveness of diabetes prevention interventions

  - Effective ways to deliver preventive interventions

결 론

- 임신성 당뇨병의 진단과 치료는 주산기 합병증을 감소시킨다.

- 임신성 당뇨병 여성은 분만 후 정기적인 혈당검사를 시행하고 당뇨병의 위험성에 대한 설명과 예방을 위한 생활 요법이 필요하다.

- 임상의는 임신성 당뇨병 여성에게 당뇨와 심혈관질환 위험인자의 조기발견, 예방과 관리에 대한 최신지견을 적용함으로써 이들의 삶을 향상시킬 수 있다.