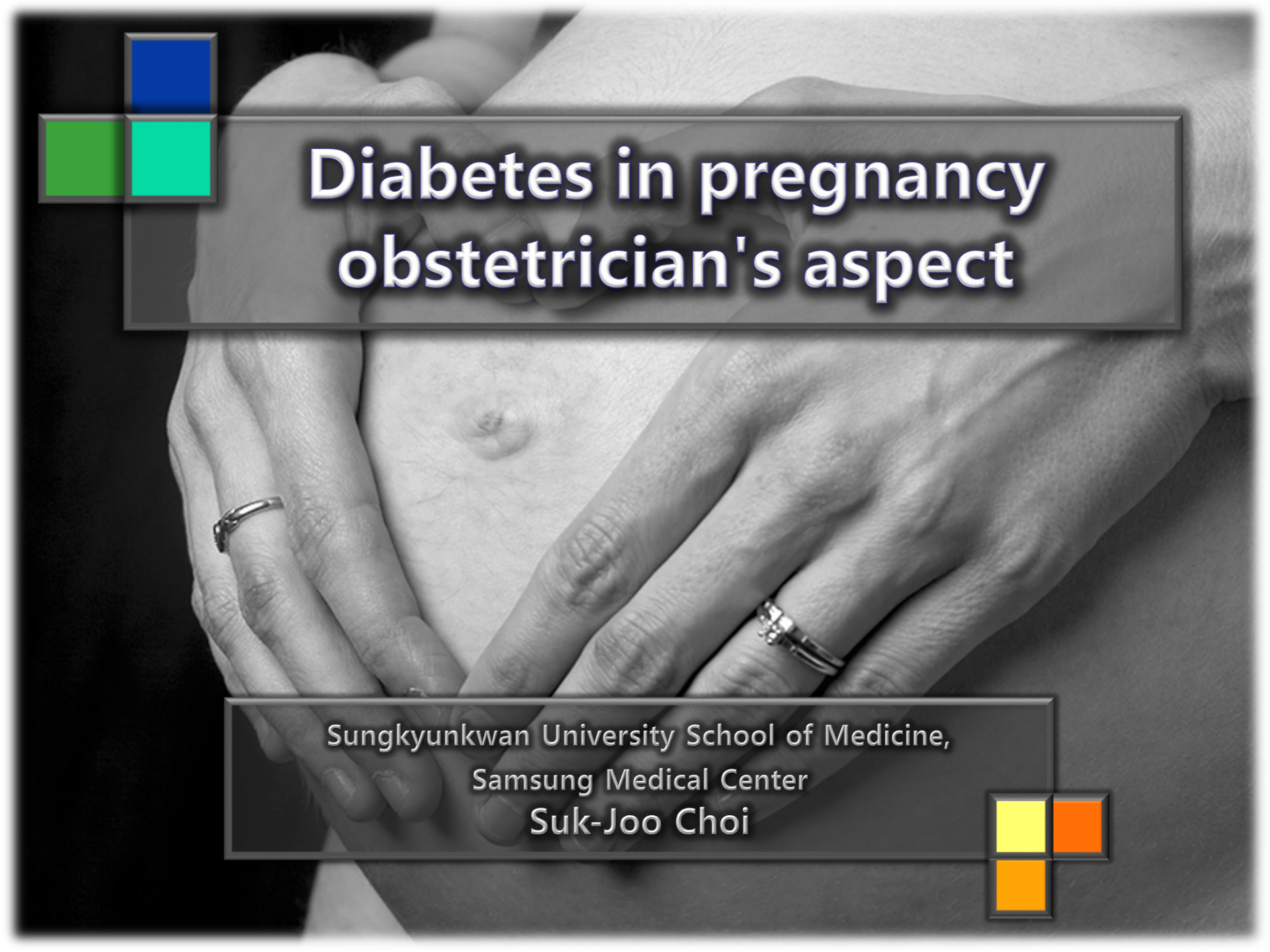
Diabetes in pregnancy obstetrician's aspect



Sungkyunkwan University School of Medicine,
Samsung Medical Center
Suk-Joo Choi

본 발표와 관련된 이해관계

없 음

Diabetes during pregnancy

- **Classification**

  1) Pregestational DM (PGDM): overt DM (type 1 & type 2 DM)

  2) Gestational DM (GDM): carbohydrate intolerance of variable severity with onset or first recognition during pregnancy

- Both type 2 diabetes and GDM are characterized by insulin resistance and a relative insulin deficiency

TABLE 57-3. Proposed Classification System for Diabetes in Pregnancy

Gestational diabetes: diabetes diagnosed during pregnancy that is not clearly overt (type 1 or type 2) diabetes

Type 1 Diabetes:	**Type 2 Diabetes:**
Diabetes resulting from β-cell destruction, usually leading to absolute insulin deficiency	Diabetes from inadequate insulin secretion in the face of increased insulin resistance
a. Without vascular complications	a. Without vascular complications
b. With vascular complications (specify which)	b. With vascular complications (specify which)

Other types of diabetes: genetic in origin, associated with pancreatic disease, drug-induced, or chemically induced

Data from American Diabetes Association, 2012.

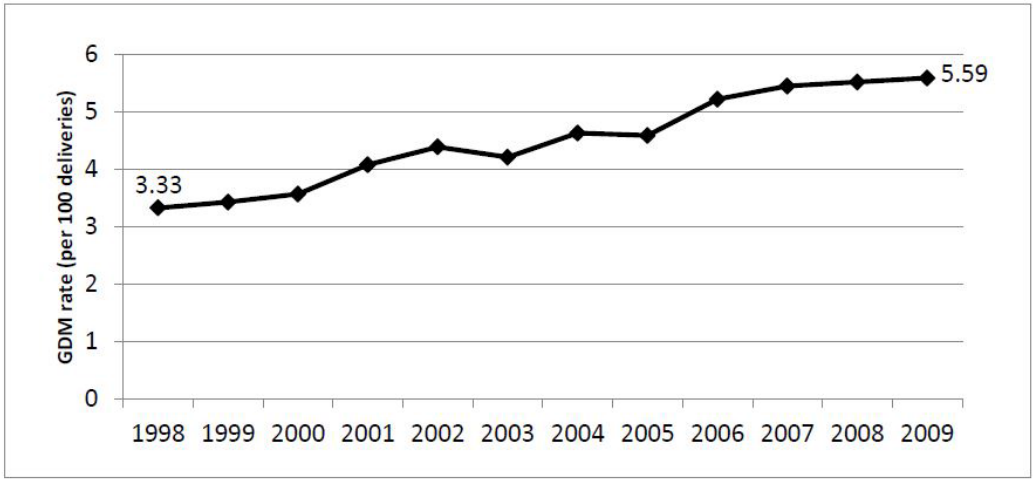
Diabetes Care 2017;40(Suppl. 1):S11–S24

Diabetes during pregnancy

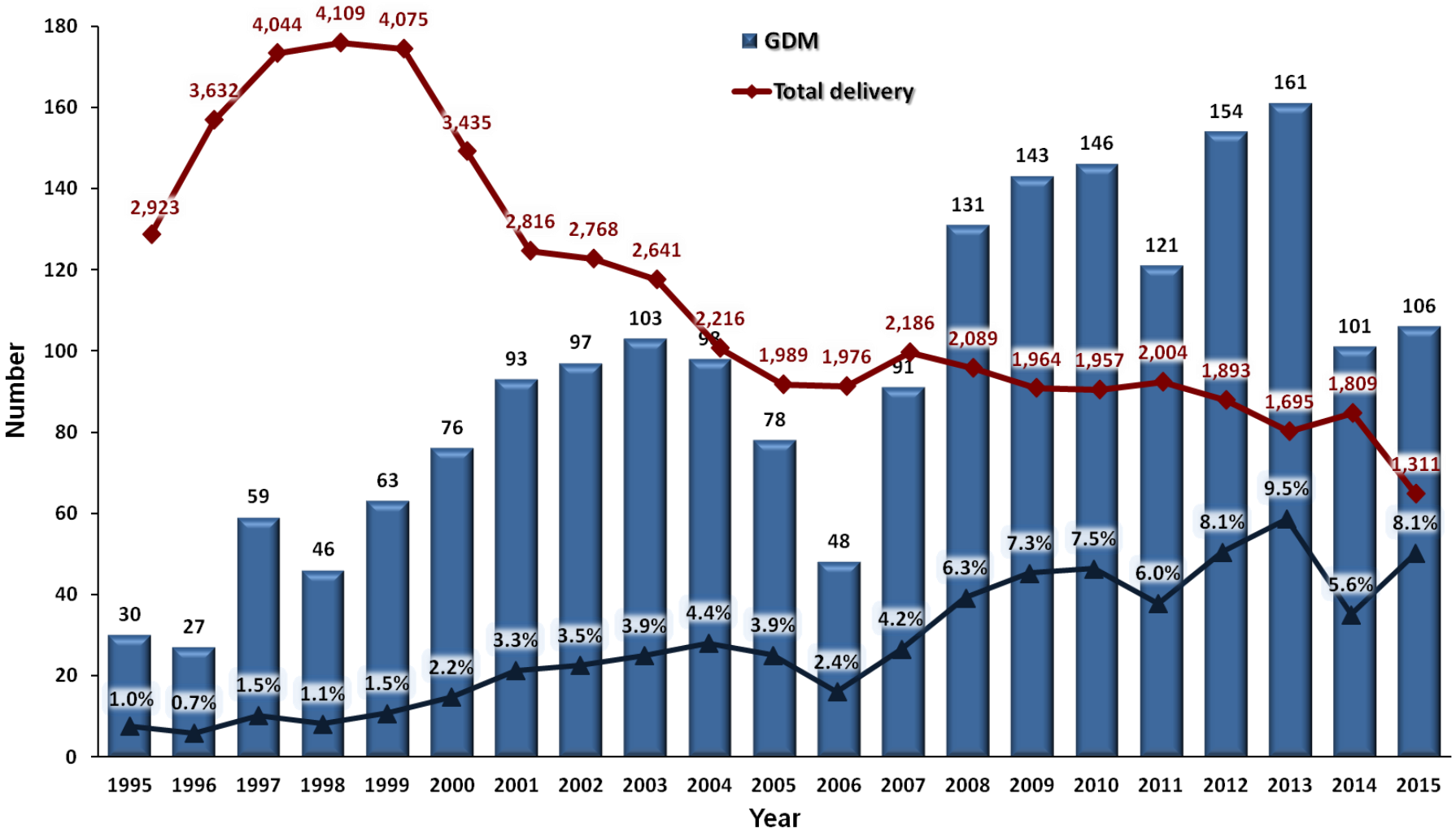
- **Increasing incidence of diabetes during pregnancy**
  1) Increasing type 2 diabetes in general population (esp, young people)
  2) Increasing obesity prevalence
  3) Increasing maternal age
  4) Evolution of diagnostic criteria

- **Major economic burden for the public health care system**

Figure 1. Rate of Gestational Diabetes Mellitus (per 100 Deliveries), 1998–2009, United States, Nationwide Inpatient Sample



Incidence of GDM in SMC OBGY



Impacts of diabetes on pregnancy

Maternal

Hypertension (preeclampsia, eclampsia)
Polyhydramnios
Preterm labor
Genital tract trauma
Operative delivery
C/S
Infection
Recurrent GDM
Diabetic nephropathy, retinopathy, neuropathy, ketoacidosis
T2DM in the future

Fetal

Abortion
Congenital anomaly (CNS (NTD), heart, GI, urogenital, others)
Unexplained fetal death
Preterm birth
Macrosomia

Neonatal

Shoulder dystocia
Birth trauma
Clavicle fracture
Brachial plexus injury
RDS
Hypoglycemia
Hypocalcemia
Hyperbilirubinemia
Polycythemia
Cardiac hypertrophy
Inheritance of diabetes
Long-term cognitive development

Goal of glycemic control during pregnancy

- **Minimize the complications of diabetes during pregnancy**
- **Maintain blood glucose levels as close to normal as possible, avoiding hyoglycemia**
- **Normoglycemia can be achieved by**

① Diet

② Exercise

③ Drug (insulin, oral hypoglycemic agents)

Screening & diagnosis of GDM

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 h after the load is ≥130 mg/dL, 135 mg/dL, or 140 mg/dL* (7.2 mmol/L, 7.5 mmol/L, or 7.8 mmol/L), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan (59)	or	NDDG (60)
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NIH (2013) ACOG (2013)

Diabetes Care 2017;40(Suppl. 1):S11–S24

Screening & diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24−28 weeks of 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 met or 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)

"these newer criteria resulted in a considerable increase in prevalence of GDM..."

IADPSG (2010) | ADA (2011)

Diabetes Care 2017;40(Suppl. 1):S11–S24

Screening & diagnosis of GDM

Introduction of IADPSG Criteria for the Screening and Diagnosis of Gestational Diabetes Mellitus Results in Improved Pregnancy Outcomes at a Lower Cost in a Large Cohort of Pregnant Women: The St. Carlos Gestational Diabetes Study

Alejandra Duran,[1,2] Sofía Sáenz,[1] María J. Torrejón,[3] Elena Bordiú,[1,2] Laura del Valle,[1] Mercedes Galindo,[1] Noelia Perez,[4] Miguel A. Herraiz,[2,4] Nuria Izquierdo,[4] Miguel A. Rubio,[1,2] Isabelle Runkle,[1,2] Natalia Pérez-Ferre,[1] Idalia Cusihuallpa,[1] Sandra Jiménez,[1] Nuria García de la Torre,[1] María D. Fernández,[1] Carmen Montañez,[1] Cristina Familiar,[1] and Alfonso L. Calle-Pascual[1,2]

Diabetes Care 2014;37:2442–2450 | DOI: 10.2337/dc14-0179

The use of IADPSGC resulted in an important increase in GDM rate (35.5% vs. 10.6%) and an improvement in pregnancy outcomes: gestational hypertension, prematurity, cesarean section, small for gestational age, large for gestational age, Apgar 1-min score <7, and admission to NICU

Discrepancies of diagnosis & management of GDM

Table 1 Comparison between NICE, ADA and ACOG guidelines for gestational diabetes

Item	ADA	ACOG	NICE
Who should be screened for GDM	Women at high risk of GDM should undergo GTT as soon as feasible. If found not to have GDM at initial screening, they should be retested between 24 and 28 weeks. Women of average risk should have testing undertaken at 24–28 weeks. Low-risk status requires no glucose testing,	Because only 10% of the population would be exempt from screening using the selective method, the ACOG suggests that screening all pregnant women (universal screening) may be a more practical approach.	BMI 30+ kg/m^2, previous baby 4.5+kg, previous GDM, 1st degree relative with diabetes, South Asian, black Caribbean, Middle Eastern Not included: age, other high risk ethnic groups, past impaired glucose tolerance (IGT), polycystic ovarian syndrome
What women should be told about screening and testing for GDM	Although uncomplicated GDM with less severe fasting hyperglycemia has not been associated with increased perinatal mortality, GDM of any severity increases the risk of fetal macrosomia.	Women with GDM are more likely to develop hypertensive disorders than women with out GDM. GDM increases the risk of fetal macrosomia In addition; women with GDM have an increased risk of developing diabetes later in life.	Most women respond to diet/exercise; some (10-20%) need other agents; if GDM is not detected, there is a small risk of birth complications such as shoulder dystocia; GDM may lead to more interventions
How screening for GDM should occur	Women with high risk of GDM, GTT as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women of average risk should have testing undertaken at 24–28 weeks of gestation. Low-risk status requires no glucose testing,	Universal screening by 2-step method. It involves an initial test after administration of 50 g of glucose one -hour test followed by an GTT to confirm the diagnosis for patients with an abnormal initial result	75g 2 hour OGTT at 16-18 weeks if prior GDM; 24-28 weeks if risk factors.
Criteria for GDM	100 g glucose: Plasma glucose level: (2 or more time points need to elevated) Fasting, > 5.3mmol/L 1-hour, > 10.0mmol/L; 2-hour, > 8.6mmol/L; (only 2h if 75 g of glucose used) 3-hour, > 7.8mmol/L	100g glucose Plasma glucose level: (2 or more time points need to elevated) Fasting >5.3mmol/L; 1-hour, > 10.0mmol/L; 2-hour, > 8.6mmol/L; 3-hour, > 7.8mmol/L	75g glucose Plasma glucose level: (1 or more time points need to elevated) Fasting 7.0 mmol/l; 2 hour 7.8 mmol/l
Screening for undiagnosed T2DM	High risk of GDM should undergo GTT as soon as feasible	The diagnosis of diabetes recommended in the first half of	Early testing of blood glucose or OGTT for women with a history of

Discrepancies of diagnosis & management of GDM

Table 1 Comparison between NICE, ADA and ACOG guidelines for gestational diabetes

Item	ADA	ACOG	NICE
Targets for blood glucose control	Fasting whole blood glucose ≤5.3 mmol/l 1-h postprandial whole blood glucose ≤ 7.8mmol/l 2-h postprandial whole blood glucose ≤ 6.7 mmol/l	Plasma glucose level: Fasting, ≤5.3 mmol/l 1-hour postprandial, ≤ 7.2	Fasting 3.5-5.9 mmol/l 1 hour postprandial <7.8 mmol/l. No HbA1c 2nd/3rd trimester
GDM antenatal management	All women with GDM should receive nutritional counseling. BMI >30 kg/m^2, a 30–33% calorie restriction to ~25 kcal/kg actual weight per day. Selection of pregnancies for insulin therapy can be based on measures of maternal glycaemia with or without assessment of fetal growth characteristics. Inadequate information to recommend oral hypoglycaemic agents	Nutritional intervention in women with GDM should be designed to achieve normal glucose levels to avoid ketosis. Hypoglycaemic therapy supported by ACOG: further studies recommended for glyburide. Insulin therapy based on measures of maternal glycaemia based on fasting, 1 and 2 hours postprandial	Low GI Diet, calorie restriction if BMI 27+ kg/m^2, moderate exercise, hypoglycaemic therapy (including metformin) after 1-2 weeks if lifestyle insufficient or Abdominal circumference >70th centile at diagnosis
GDM intrapartum management	Delivery during the 38th week is recommended unless obstetric considerations dictate otherwise. Prolongation of gestation past 38 weeks increases the risk of fetal macrosomia without reducing cesarean rates	The timing of delivery in GDM remains relatively open. If estimated fetal weight of 4,500 g or more, cesarean delivery may be considered.	Induce/elective caesarean after 38 weeks if normally grown fetus; glucose monitoring hourly-target 4-7 mmol/l if higher-intravenous dextrose/insulin
GDM postpartum management	All patients with prior GDM should be educated regarding lifestyle modifications, including maintenance of normal body weight. Patients should be advised to seek medical attention if they develop symptoms of hyperglyceamia	Individuals at increased risk of T2DM (i.e obesity, increase age at the diagnosis of GDM) Should be counseled regarding diet, exercise, and weight reduction or maintenance to delay or prevent T2DM	Women should have blood glucose tested before discharge, be reminded of symptoms of hyperglycaemia, offered lifestyle advice and advised of risk of GDM in future pregnancy
GDM postnatal testing	If glucose levels are normal post-partum, reassessment of glyceamia should be undertaken at a minimum of 3-year intervals. Women with IFG or IGT in the postpartum period should be tested for diabetes annually	All women with GDM be screened at 6-12 weeks postpartum, either fasting blood glucose or 75 g GTT. If GTT/FBG normal assess every 3 years. Consider metformin in IFG and IGT.	FBG at 6 weeks (but not an OGTT) and annually thereafter

Current practice pattern

PGDM

IM

Glycemic control

Pregnancy

IM

Glycemic control

OBGY

Delivery

Pregnant women

OBGY

GDM

IM

Glycemic control

VS

OBGY

Glycemic control

Delivery

Major points of concern: IM vs. OBGY

Maternal

Hypertension (preeclampsia, eclampsia)
Polyhydramnios
Preterm labor
Genital tract trauma
Operative delivery
C/S
Infection
Recurrent GDM
Diabetic nephropathy, retinopathy, neuropathy, ketoacidosis
T2DM in the future

Fetal

Abortion
Congenital anomaly (CNS (NTD), heart, GI, urogenital, others)
Unexplained fetal death
Preterm birth
Macrosomia

Neonatal

Shoulder dystocia
Birth trauma
Clavicle fracture
Brachial plexus injury
RDS
Hypoglycemia
Hypocalcemia
Hyperbilirubinemia
Polycythemia
Cardiac hypertrophy
Inheritance of diabetes
Long-term cognitive development

Major points of concern: IM vs. OBGY

Maternal

Hypertension (preeclampsia, eclampsia)
Polyhydramnios
Preterm labor
Genital tract trauma
Operative delivery
C/S
Infection
Recurrent GDM

IM

Diabetic nephropathy, retinopathy, neuropathy, ketoacidosis
T2DM in the future

Fetal

Abortion
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OBGY

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Hypoglycemia
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Cardiac hypertrophy
Inheritance of diabetes
Long-term cognitive development

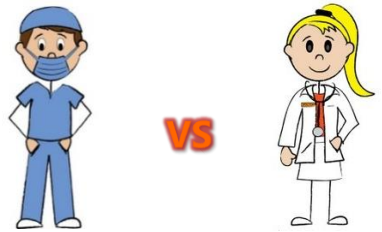
IM vs. OBGY

Korean Journal of Obstetrics and Gynecology
Vol. 51 No. 7 July 2008

임신 중 당뇨의 조절은 어느 과에서 시행하는 것이 적절한가?: 내과와 산부인과에서의 비교

을지대학교 의과대학 을지병원 산부인과

서용수 · 신정환 · 이헌열 · 박원일 · 김재령
김혜민 · 최은주 · 김대운 · 홍서유 · 박은주



OBGY IM

Who is more appropriate to do metabolic control of pregnancy complicated by diabetes?: Comparison of internist and obstetrician

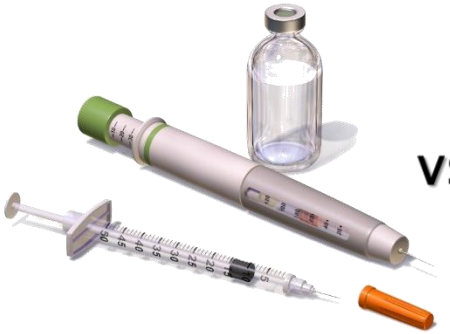
Yong Soo Seo, M.D., Jung Hwan Shin, M.D., Hun Yul Lee, M.D., Won Il Park, M.D., Jae Ryung Kim, M.D., Hae Min Kim, M.D., Eun Joo Choi, M.D., Dae Woon Kim, M.D., Seo Yoo Hong, M.D., Eun Ju Park, M.D.

Department of Obstetrics and Gynecology, Eulji University School of Medicine, Eulji General Hospital, Seoul, Korea

Today's topics

SMBG

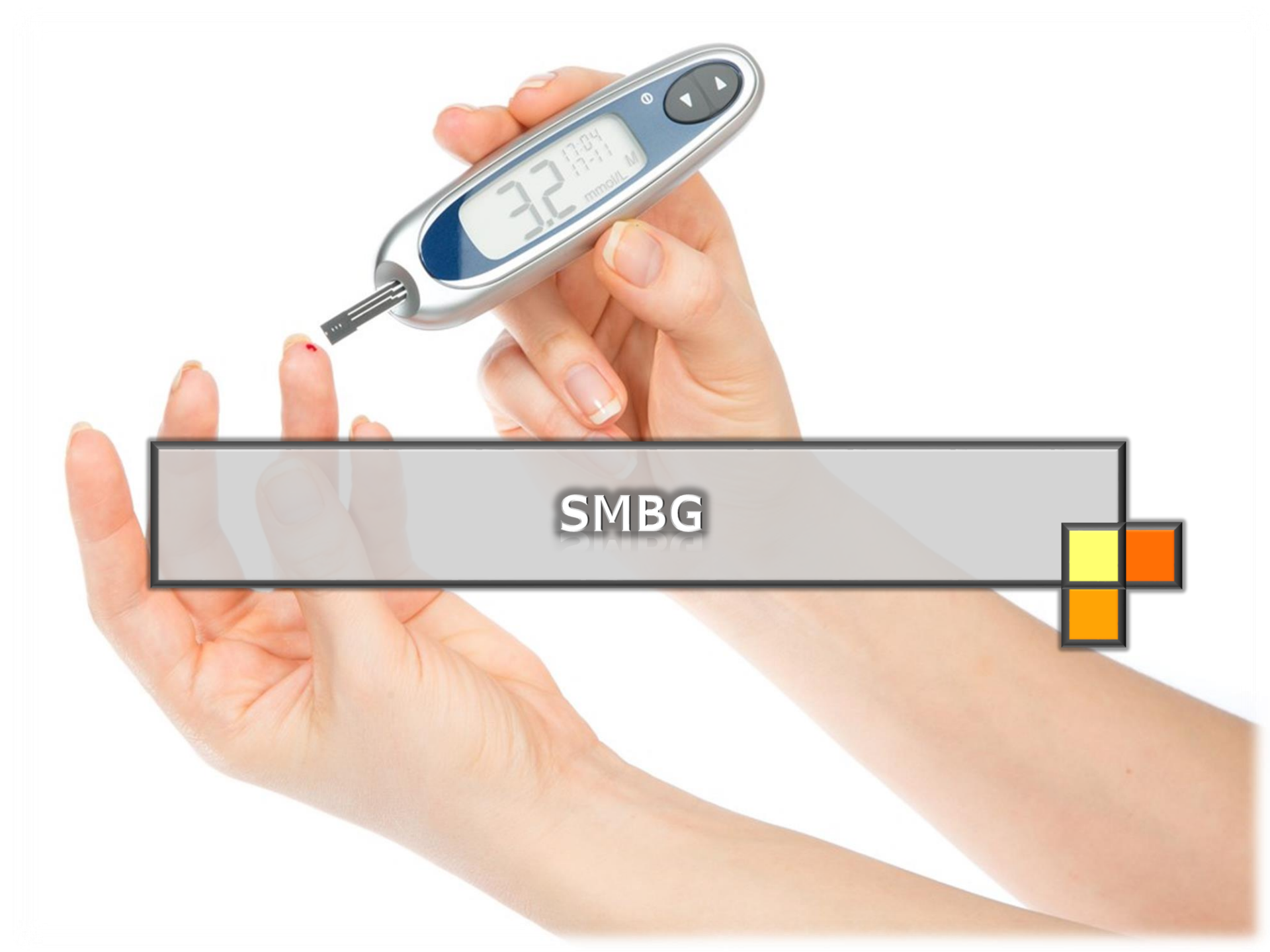
Target BSL



vs.

Insulin vs. OHA

Postpartum surveillance



SMBG

Self-monitoring blood glucose (SMBG)

- SMBG is a essential component of effective therapy
- Adjust nutrition therapy, physical activity and medication
- 4 times daily, fasting and either PP1 or PP2
- Once well controlled by her diet, the frequency of monitoring can be modified
- There is no evidence from randomized controlled trials to support any specific glucose measurements timing and frequency

Diabetes Care Volume 37, Supplement 1, 2014

Preprandial vs. postprandial

The New England
Journal of Medicine

Volume 333 NOVEMBER 9, 1995 Number 19

POSTPRANDIAL VERSUS PREPRANDIAL BLOOD GLUCOSE MONITORING IN WOMEN WITH GESTATIONAL DIABETES MELLITUS REQUIRING INSULIN THERAPY

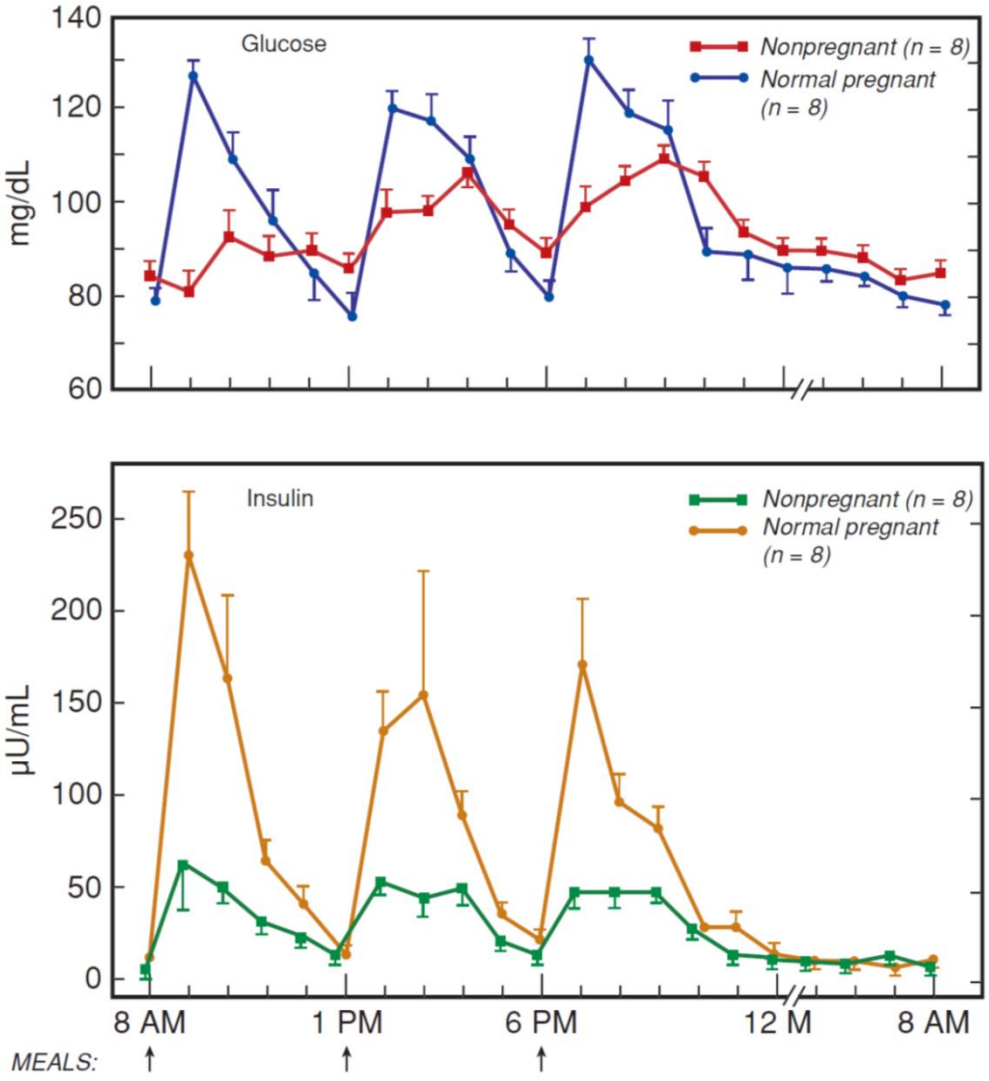
MARGARITA DE VECIANA, M.D., CAROL A. MAJOR, M.D., MARK A. MORGAN, M.D., TAMEROU ASRAT, M.D., JULIANNE S. TOOHEY, M.D., JEAN M. LIEN, M.D., AND ARTHUR T. EVANS, M.D.

- Adjustment of insulin therapy in women GDM according to the results of **postprandial 1-hr BSL** (FBS, PP1 every meal) , rather than **preprandial BSL** (FBS, preprandial & bed-time)

➔ improved glycemic control &

↓ neonatal hypoglycemia, ↓ macrosomia, ↓ cesarean delivery for CPD

Physiologic change during pregnancy



Pregnancy is potentially diabetogenic

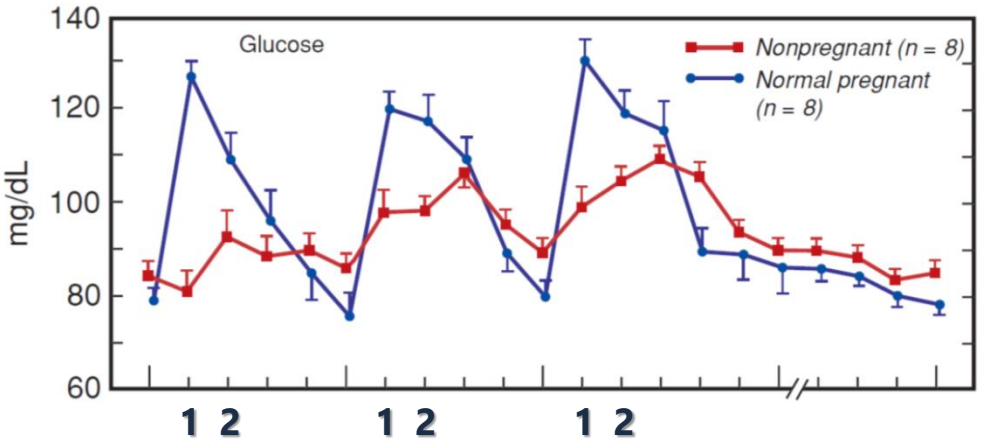
- Mild fasting hypoglycemia
- Postprandial hyperglycemia (peak at 1 hour)
- Postprandial hyperinsulinemia
- Peripheral insulin resistance

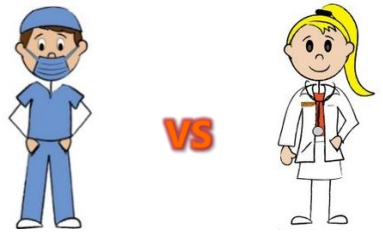
➔ Sustained postprandial supply of glucose to the fetus

"Accelerated starvation state"

PP1 vs. PP2

- PP1 is better than PP2 for predicting neonatal outcome?





The New England Journal of Medicine

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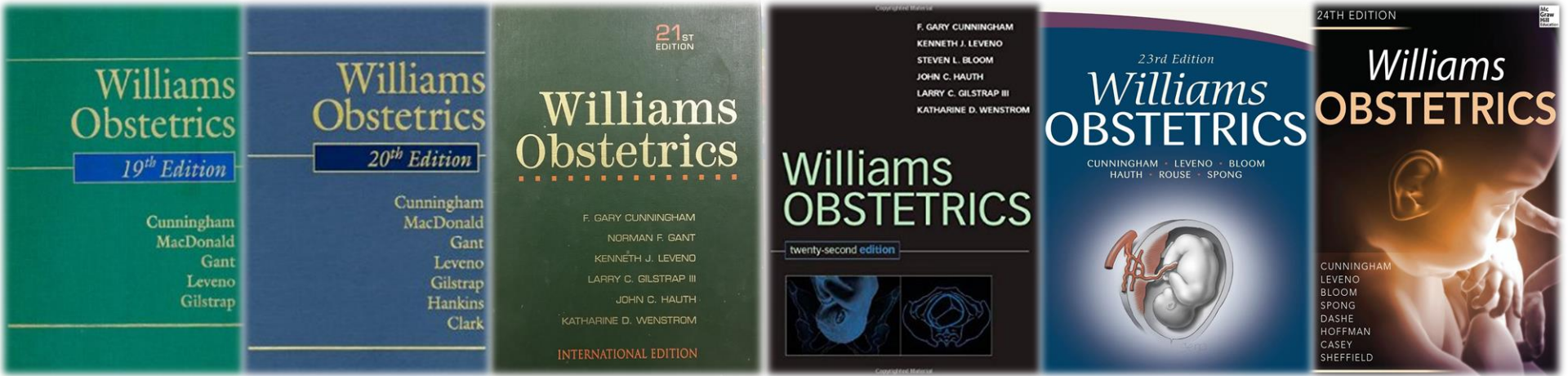
MARGARITA DE VECIANA, M.D., CAROL A. MAJOR, M.D., MARK A. MORGAN, M.D., TAMEROU ASRAT, M.D., JULIANNE S. TOOHEY, M.D., JEAN M. LIEN, M.D., AND ARTHUR T. EVANS, M.D.



PP1 vs. PP2

- The fetal birthweight, percentage of women requiring insulin and the total daily dose of insulin were similar in PP1 & PP2 measurement groups.

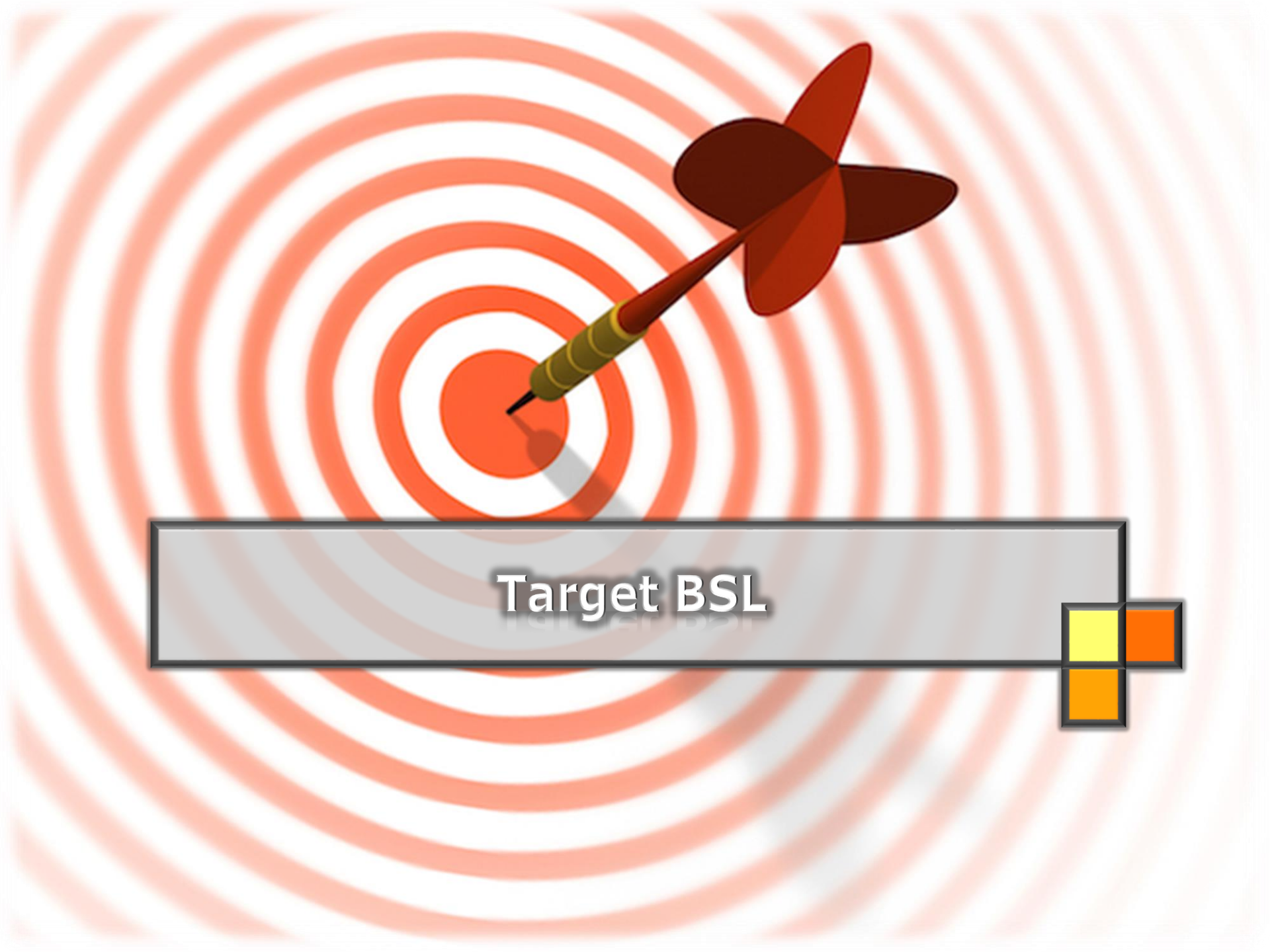
Moses RG et al. ANZJOG 1999

- PP1 and PP2 plasma glucose measurements were not superior to each other in predicting fetal macrosomia or perinatal complications.

Ozgu-Erdinc AS et al. Endocrine 2016

- Women with GDM managed by PP1 measurements is associated with a decreased rate of insulin therapy. However, neonatal and obstetrical outcomes are not determined by the timing of their glucose determinations.

Weisz B et al. J Perinatol 2005


Target BSL

Target BSL (PGDM vs. GDM)

	Pre-existing diabetes	Gestational diabetes
Fasting and Before Meal	60-99	less than 96
After Meal (1 hr-2 hr)	100-129	
After Meal (2 hr)		less than 120
A1c	less than 6.0%	

Amounts shown above mg/dL

These are general medical guidelines.Please follow your doctor's instructions.

Target BSL for GDM

Table 1 Recommended capillary blood glucose target values for patients with gestational diabetes mellitus

	ACOG (mg/dl)	ADA	NICE	FIGO
Fasting glucose	<95	<95	<95	<95
1-h post prandial glucose	<130–140	<140	<140	<140
2-h post prandial glucose	<120	<120	<115	<120

ACOG American Congress of Obstetricians and Gynecologists, *ADA* American Diabetes Association, *NICE* National Institute for Health and Care Excellence, *FIGO* International Federation of Gynecology and Obstetrics

Bergel R et al. Curr Diab Rep 2016

HAPO study

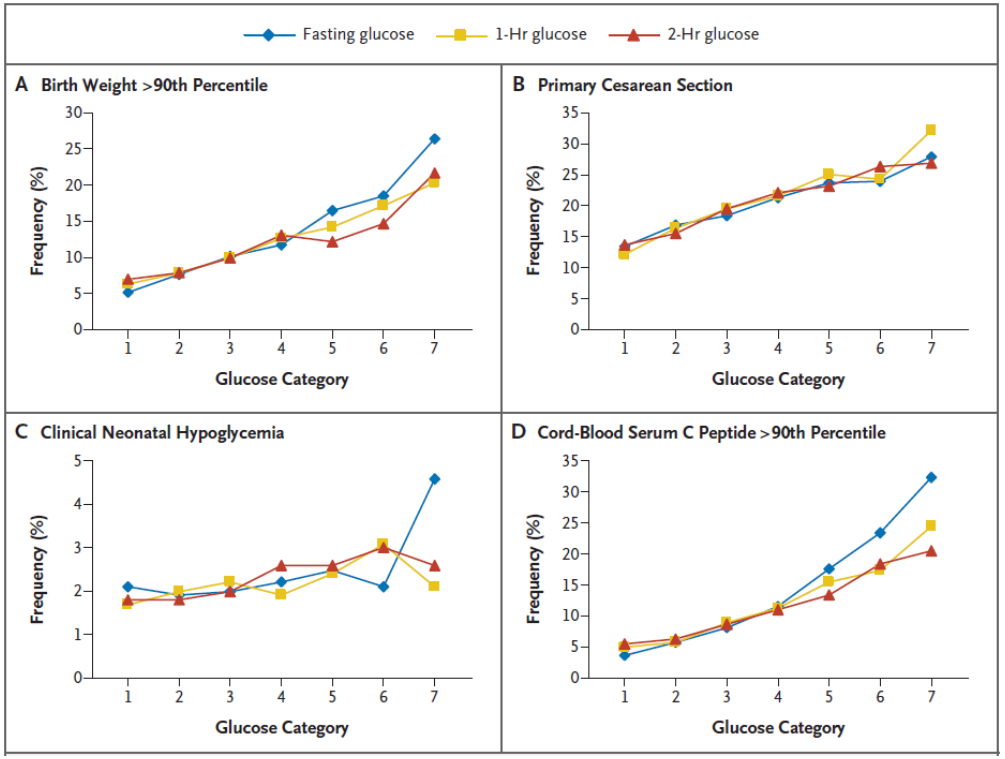
- Continuous association between increasing maternal plasma glucose levels and adverse pregnancy outcomes:
  PTD, preeclampsia, birth injury, shoulder dystocia, NICU admission, hyperbilirubinemia
- Led to reconsider current criteria for diagnosing and treating hyperglycemia during pregnancy
  ➔ **towards lowering the threshold ?**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 8, 2008 VOL. 358 NO. 19

Hyperglycemia and Adverse Pregnancy Outcomes

The HAPO Study Cooperative Research Group*



Effect of treatment of GDM

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 16, 2005 VOL. 352 NO. 24

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*

- Reduction of serious perinatal complication (death, shoulder dystocia, bone fracture, nerve palsy) (1% vs. 4%; aRR 0.33; 95% CI 0.14 to 0.75; P=0.01)
- Improve the woman's health-related quality of life
- ↓ Birth weight, ↓ large for gestational age (LGA), ↓ macrosomia

Treatment of mild GDM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

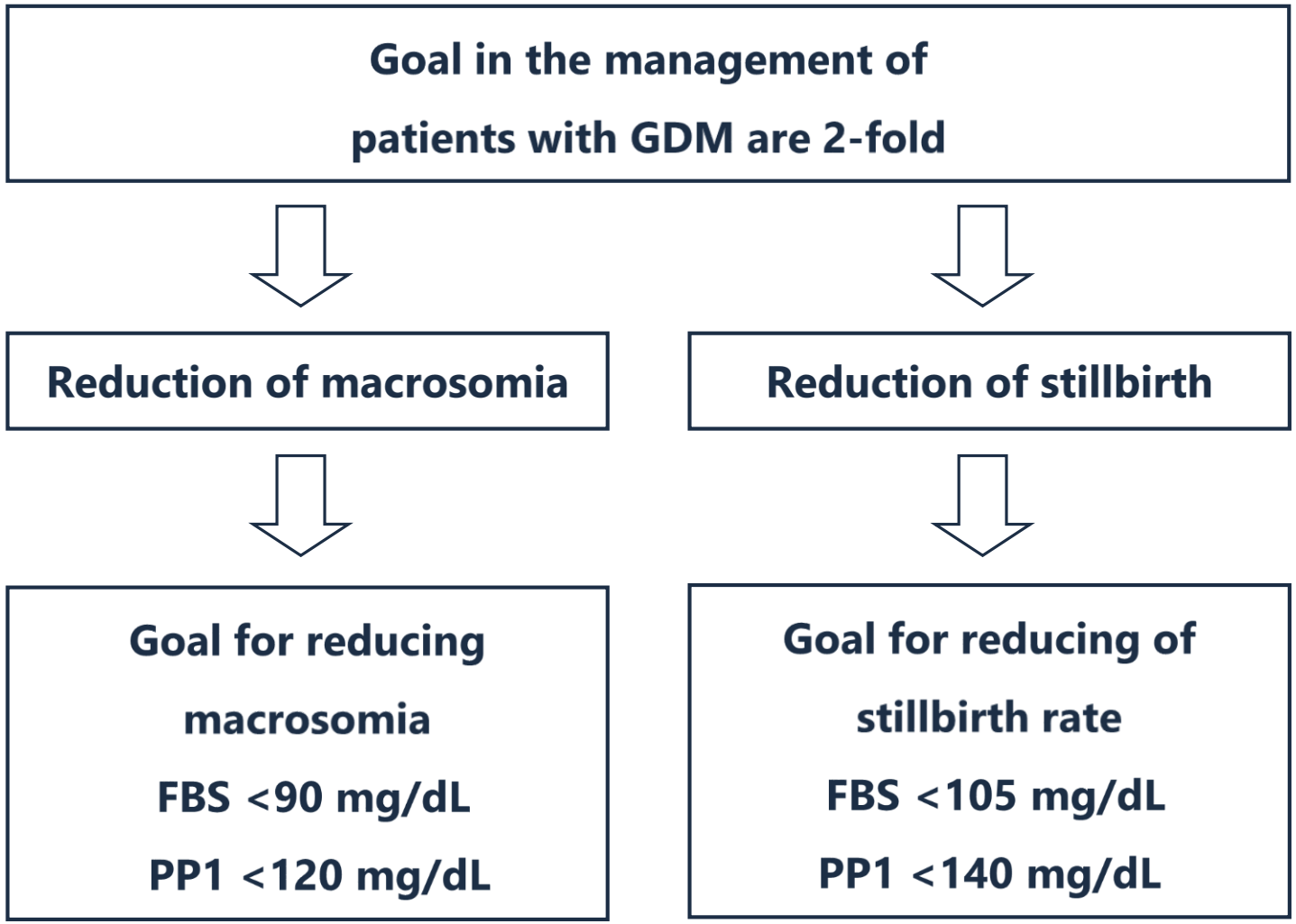
A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes

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*

N Engl J Med 2009;361:1339-48.

- No differences in primary composite outcome: perinatal death, neonatal hypoglycemia, elevated umbilical cord C-peptide level, or birth trauma
- ↓ LGA, ↓ birth weight >4 Kg, ↓ neonatal fat mass, ↓ C/S, ↓ shoulder dystocia, ↓ hypertensive disorders

Target BSL



Combs, Diabetes Care, 1992

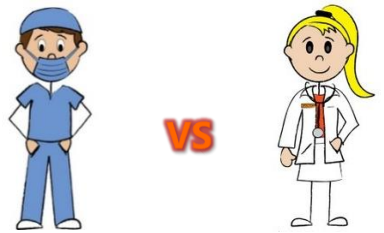
IM vs. OBGY

Korean Journal of Obstetrics and Gynecology
Vol. 51 No. 7 July 2008

임신 중 당뇨의 조절은 어느 과에서 시행하는 것이 적절한가?: 내과와 산부인과에서의 비교

을지대학교 의과대학 을지병원 산부인과

서용수 · 신정환 · 이헌열 · 박원일 · 김재령
김혜민 · 최은주 · 김대운 · 홍서유 · 박은주



- Retrospective analysis of 72 women with diabetes (PGDM, GDM)
- Overall similar maternal & neonatal outcome (C/S, gestational age at delivery, preeclampsia, infection, etc.)
- OBGY group: ↓ Birth weight, ↓ LGA (>3.8 Kg), ↓ low 1 min Apgar score

IM vs. OBGY

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CLINICAL ARTICLE

A Korean multicenter study of prenatal risk factors for overt diabetes during the postpartum period after gestational diabetes mellitus

Na-Ri Shin [a], So-Yeon Yoon [a], Geum Joon Cho [b], Suk-Joo Choi [a], Han-Sung Kwon [c], Soon Cheol Hong [b], Ja-Young Kwon [d], Soo-young Oh [a,*]

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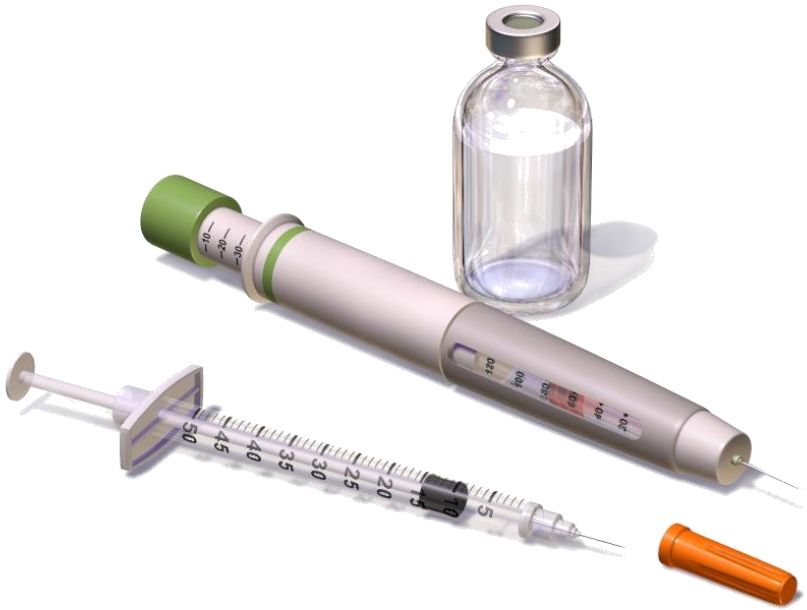
[c] Department of Obstetrics and Gynecology, Konkuk University School of Medicine, Seoul, South Korea
[d] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea

	A (n=609)	B (n=291)	C (n=508)	D (n=190)
Mean HbA1C (during pregnancy)	5.49%	5.87%	6.14%	5.78%
Macrosomia >4.0 kg	3.9%	10.7%	12.8%	7.4%
Cesarean section	47.5%	58.4%	66.1%	55.3%

Insulin vs. OHA



Glycemic control of PGDM and GDM

- **PGDM**

  1) Continue glycemic control before pregnancy & throughout pregnancy

  2) Multiple daily insulin injections and adjustment of dietary intake

  3) Metformin is often continued during pregnancy and insulin is added as appropriate to the therapy

- **GDM**

  1) Diet & exercise

  2) If glycemic control is not achieved solely by diet, then pharmacological treatment is indicated: insulin or oral hypoglycemic agent

Pharmacological treatment for GDM

- Insulin, glyburide, and metformin are safe and effective therapies for GDM during the second and third trimesters.
- They may be initiated as first-line treatment after failing to achieve glucose control with lifestyle modification.

  (FBS >95 mg/dL, PP1 >140 mg/dL or PP2 >120 mg/dL)
- Among oral medication therapy, metformin may be a better choice than glyburide.

FIGO GDM Initiative's Recommendations for pharmacological treatment in women with GDM. IJGO 2015

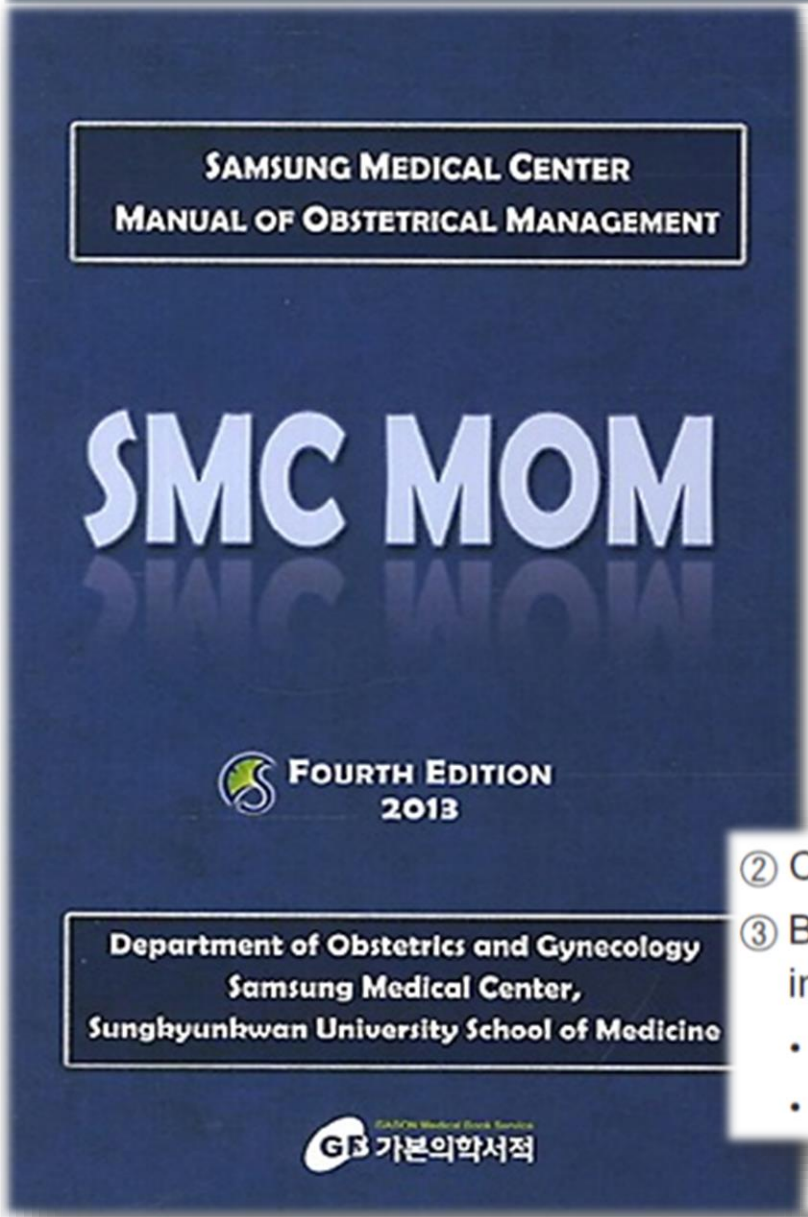
Insulins

- Rapid-acting insulin should be combined with intermediate/long-acting insulin, to simulate physiological insulin secretion throughout the day
- No evidence supports one regimen over another as being superior in terms of glycemic control, patient safety and pregnancy outcome

Table 3 Insulin duration of action profile

Insulin type	Onset of action	Peak of action	Duration of action
Lispro	10–15 min	1–2 h	4–5 h
Aspart	10–15 min	1–2 h	4–5 h
Glulisine	10–20 min	30–90 min	4–5 h
Regular	30–60 min	2–4 h	6–8 h
NPH	1–3 h	5–7 h	13–18 h
Glargine	1–2 h	No peak	24 h
Detemir	1–2 h	No peak	24 h

Insulin treatment regimen in SMC



3. Inpatient management

Insulin therapy

1) Criteria for insulin treatment [20]

① Fasting BSL > 95 mg/dL or
② 1-hour postprandial BSL > 130~140 mg/dL or
③ 2-hour postprandial BSL > 120 mg/dL despite standard diet therapy

2) Total daily dose (TDD) in each trimester [21]

① 1st trimester : 0.7~0.8 U/kg/day
② 2nd trimester : 0.8~1.0 U/kg/day
③ 3rd trimester : 0.9~1.2 U/kg/day
④ Massive obese : 1.5~2.0 U/kg/day

3) Regimen

① Starting dose
- 2/3 of TDD: AM insulin (
- 1/3 of TDD: PM insulin (

② Add short-acting insulin
③ Starting dose may be d
profile without insulin th
④ Bedtime (10P) NPH d
injection given with the
of nocturnal hypoglycemia and Somogi phenomenon

Recent trend

RI ➔ Insulin aspart or lispro

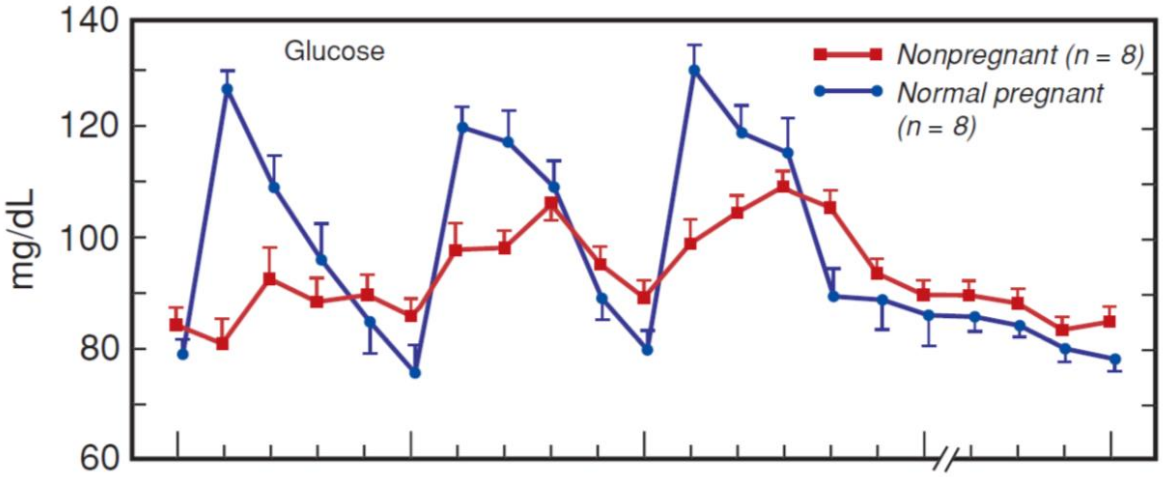
NPH ➔ Detemir

② Choice of insulin and its regimen should be individualized

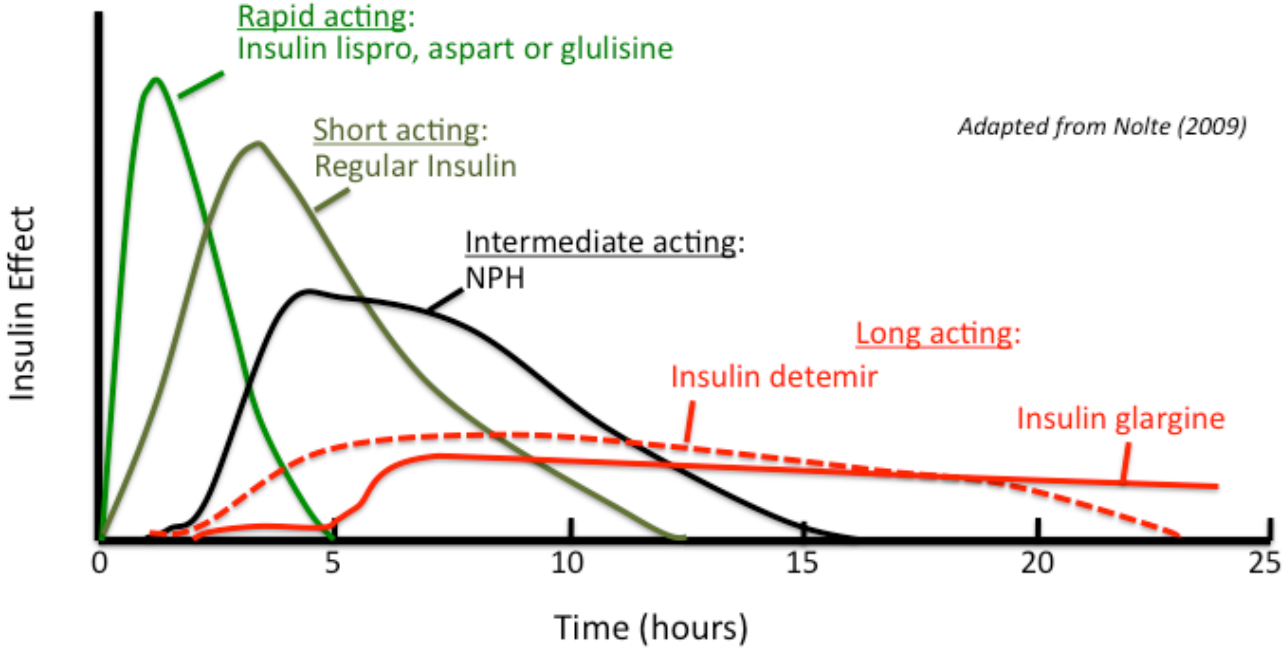
③ Benefits of insulin lispro and aspart (compared to regular insulin) [21]
- More rapid onset of action
- Lower risk of delayed postprandial hypoglycemia

minutes before meal and
- Insulin lispro and aspart should be given immediately before meal

Rapid vs. regular insulin



- Mild fasting hypoglycemia
- Postprandial hyperglycemia (peak at 1 hour)



Rapid vs. regular insulin

Original Article

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Published online: October 17, 2015

Pregnancy and Neonatal Outcomes in Gestational Diabetes Treated with Regular Insulin or Fast-Acting Insulin Analogues

Ji Yeon You Suk-Joo Choi Cheong-Rae Roh Jong-Hwa Kim Soo-young Oh

Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

- Retrospective analysis of 197 women with GDM who needed insulin therapy
- No differences in maternal & neonatal outcome: C/S, gestational age at delivery, preeclampsia, infection, birth weight, macrosomia, NICU admission, neonatal hypoglycemia

Insulin lispro vs. regular insulin

- Potential for improved glycemic control with rapid acting analogues compared to regular insulin

Table II. Impact of lispro on blood glucose control in pregnancies complicated by diabetes.

Author	*N* =	Diabetes type	Glycemic outcomes
Jovanovic (1999)	Lispro = 19 Regular = 23	GDM	No differences in A1c but area under the curve for glucose, insulin and C-peptide significantly lower in lispro group
Buchbinder (2000)	Lispro = 12 Regular = 42	Type 1	No differences in A1c
Bhattacharyya (2001)	Lispro = 75 Regular = 138	GDM and	Pre-delivery A1c significantly lower in lispro group
	Lispro = 27 Regular = 70	Type 1 and type 2	No differences in A1c
Persson (2002)	Lispro = 16 Regular = 17	Type 1	No differences in A1c but blood glucose levels after breakfast significantly lower in lispro group
Loukovaara (2003)	Lispro = 36 Regular = 33	Type 1	A1c levels significantly lower in lispro group
Mecacci (2003)	Lispro = 25 Regular = 24	GDM	Postprandial glucose levels significantly lower in the lispro group
Cypryk (2004)	Lispro = 25 Regular = 46	Type 1 and type 2	No differences in A1c

Homko CJ et al. J Maternal Fetal Neonatal Med 2006

Insulin aspart vs. regular insulin

- **RCT of insulin aspart vs. RI in T1DM in pregnancy:** Comparable perinatal mortality, congenital malformations, birthweight, mean gestational age, a tendency toward fewer fetal losses and preterm deliveries in the insulin aspart group

Hod M et al. AJOG 2008

- ↓ mean peak PP1 glucose in the insulin aspart group, but similar rates of maternal hypoglycemia, macrosomia, C/S

Bergel R et al. Curr Diab Rep 2016

Oral hypoglycemic agents

- Similarity between GDM and T2DM lead to the proposal that some OHAs could be used effectively and safely as alternatives to insulin therapy.
- Historically, OHAs were contraindicated during pregnancy d/t teratogenicity in case-series of first generation sulfonylureas
- Metformin & glyburide: FDA pregnancy category B

Oral hypoglycemic agents

- A survey of almost 1,400 fellows of the ACOG found that 13% were using glyburide as first-line therapy for diet failure in women with GDM *(Gabbe, 2004)*.
- Use of glyburide has exponentially increased from 7.4 to 64.5 %, from 2000 to 2011.
- Although, OHAs are being increasingly used for GDM, they have **not** been approved by the FDA on for this indication.
- NICE (2008), ACOG (2013), FIGO (2015), CDA recommend that both glyburide and metformin are appropriate, as is insulin, for glycemic control in women with GDM.
- OHAs are **not** currently recommended for overt diabetes except for limited and individualized use (ACOG, 2012).

Metformin

- A biguanide that inhibits hepatic gluconeogenesis and glucose absorption and stimulates glucose uptake in peripheral tissues.
- Crosses placenta, but no teratogenicity
- Doses: 500 mg once or twice daily with food and increased, typically over a period of 1 to 2 weeks, to meet glycemic targets up to a maximum daily dose of 2,500 mg

Metformin vs. insulin

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*

- **Metformin compared to insulin**

1) ↓ neonatal hypoglycemia, ↑ preterm births, ↑ failure rate for achieving adequate glycemic control (46.3 %)

2) Similar rate of composite neonatal morbidity (hypoglycemia, RDS, phototherapy, birth trauma, 5-min Apgar score <7 or prematurity), degree of glycemic control, umbilical cord insulin concentration

Rowan JA et al. NEJM 2008

Metformin vs. insulin

RESEARCH www.AJOG.org

OBSTETRICS

Randomized trial of metformin vs insulin in the management of gestational diabetes

Cristiane Pavão Spaulonci, MD; Lisandra Stein Bernardes, PhD; Thatianne Coutheux Trindade, MD; Marcelo Zugaib, MD, PhD; Rossana Pulcineli Vieira Francisco, MD, PhD

- **Metformin compared to insulin**

1) Adequate glycemic control with ↓ mean glucose levels throughout the day, ↓ weight gain, ↓ neonatal hypoglycemia

2) Similar rate of preeclampsia, cesarean section, and other neonatal morbidity

Spaulonci CP et al. AJOG 2013

Metformin use in GDM

Table 1. Studies of Metformin Use in GDM

Authors (Year Published)	Study Design	Study Population	No. of Subjects Treated with Metformin (n_1), Insulin (n_2), Diet Only (n_3), or Metformin + Insulin (n_4)	Outcomes Measured	Comments
Moore et al. (2007)[6]	Prospective, randomized	Women with GDM not controlled with diet and exercise	$n_1 = 32$, $n_2 = 31$	Rate of caesarean delivery, neonatal birth weight, Apgar score at 5 minutes, respiratory distress syndrome, hyperbilirubinemia, hypoglycemia, and NICU admission	All outcomes were similar between the groups
Tertti et al. (2008)[11]	Retrospective, case-control	Women with GDM	$n_1 = 45$, $n_2 = 45$, $n_3 = 85$	Maternal total weight gain, hypertension, preeclampsia, and neonatal hypoglycemia	Maternal outcomes were similar in all groups; neonatal hypoglycemia was higher in the insulin-treated group
Rowan et al. (2008)[2]	Multicenter, randomized, open-label	Women with GDM	$n_1 = 249$, $n_2 = 370$	Maternal glycemic control, maternal hypertensive complications, postpartum glucose tolerance, and treatment preference; neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score, preterm birth, and neonatal and anthropometric measures	Metformin group had less hypoglycemia but more preterm births; other outcomes were similar in both groups
Rai et al. (2009)[9]	Prospective, observational	Women with GDM	$n_1 = 30$, $n_2 = 30$	Maternal glycemic control; perinatal deaths, birth weight, and NICU admission	Metformin group had better maternal and fetal outcomes
Balani et al. (2009)[8]	Prospective, nonrandomized	Women with GDM not controlled by diet for metformin group and retrospective cohort of women with GDM for insulin group	$n_1 = 100$, $n_2 = 100$	Maternal weight gain, gestational hypertension, preeclampsia, induction of labor, and rate of caesarean section; neonatal morbidity, premature birth, neonatal jaundice, NICU admission, and macrosomia	Maternal weight gain was higher in the insulin group; other maternal outcomes and macrosomia were similar in both groups; other neonatal outcomes were improved in the metformin group

Table 1. Studies of Metformin Use in GDM, *continued from p. 290*

Authors (Year Published)	Study Design	Study Population	No. of Subjects Treated with Metformin (n_1), Insulin (n_2), Diet Only (n_3), or Metformin + Insulin (n_4)	Outcomes Measured	Comments
Ijas et al. (2010)[10]	Open-label, randomized, controlled, single-center	Women with GDM not controlled with diet	$n_1 = 50$, $n_2 = 50$	Rate of caesarean section; neonatal outcomes such as LGA status, birth weight, cord artery pH, and neonatal morbidity	No difference between the two groups for neonatal outcomes; rate of caesarean section was higher in the metformin group
Goh et al. (2011)[4]	Prospective, nonrandomized	Obese women with GDM	$n_1 = 249$, $n_2 = 399$, $n_3 = 371$, $n_4 = 216$	Rates of caesarean delivery, preterm birth, LGA, NICU admissions, and intravenous dextrose supplementation	Fewer adverse outcomes in metformin than in insulin groups
Rowan et al. (2011)[5]	Multicenter, randomized, open-label	Offspring of women with GDM who had been studied earlier	$n_1 = 154$, $n_2 = 164$	Central fat measures, total fat mass, percentage of body fat, upper arm circumference, and biceps and subcapsular skinfolds	Upper arm outcomes were higher in metformin group; other outcomes were similar in both groups
Hyer et al. (2012)[7]	Open-label, prospective	Women with GDM	$n_1 = 50$, $n_2 = 50$	Maternal weight gain, mode of delivery, and other complications; neonatal birth weight, hypoglycemia, jaundice, and birth injuries	All outcomes were similar in both groups
Spaulonci et al. (2013)[12]	Randomized, controlled, single-blind	Women with GDM not controlled by diet and exercise	$n_1 = 47$, $n_2 = 47$	Maternal weight gain; neonatal hypoglycemia	Metformin group had lower maternal weight gain and neonatal hypoglycemia
Mesdaghinia et al. (2013)[13]	Prospective, randomized	Women with GDM	$n_1 = 100$, $n_2 = 100$	Maternal A1C, weight gain, hypertension, preeclampsia, and caesarean delivery; neonatal birth weight, dystocia, 1- and 5-minute Apgar scores, neonatal sepsis, liver function tests, hypoglycemia, NICU admission, anomaly, and still birth	End of pregnancy A1C, maternal weight gain, preterm labor, neonatal jaundice, respiratory distress, and NICU admission rates were higher in the insulin group; all other outcomes were similar in both groups

Metformin vs. insulin

- **Overall similar outcome**
- **Insulin treatment:** ↑ neonatal hypoglycemia, ↑ NICU admissions rates, ↑ birth weights, ↑ maternal weight gain
- 26-46% of women required the addition of insulin

"The use of metformin in GDM is a safe alternative supported by clinical research showing no change or even improved outcomes with the use of metformin compared to insulin."

"Metformin therapy should be considered a viable alternative to insulin in the treatment of GDM."

Reece SW et al. Diabetes Spectr 2014

Glyburide

- A sulfonylurea that increases insulin secretion & insulin sensitivity of peripheral tissues
- Minimal cross the human placenta (4% ex vivo) ➔ actively transported across the placenta to the fetus (9–70 % of maternal concentrations)
- Regimen

  1) Starting dose: 2.5 mg po with morning meal (30 min ~ 1 hr before meal)
  2) If necessary, increase daily dose by 2.5 mg/day increments until 10 mg/day
  3) Then, switch to twice daily dosing until maximum of 20 mg/day reached
  4) Switch to insulin if 20 mg/day does not achieve target BSL goals

- 20-40% of women required the addition of insulin to maintain normoglycemia

Glyburide vs. insulin

The New England Journal of Medicine

VOLUME 343 OCTOBER 19, 2000 NUMBER 16

A COMPARISON OF GLYBURIDE AND INSULIN IN WOMEN WITH GESTATIONAL DIABETES MELLITUS

ODED LANGER, M.D., DEBORAH L. CONWAY, M.D., MICHAEL D. BERKUS, M.D., ELLY M.-J. XENAKIS, M.D., AND OLGA GONZALES, R.N.

- No differences in the rate of maternal and neonatal adverse outcomes between glyburide and insulin groups, with achieving comparable glycemic control and similar pregnancy outcomes.

Langer O et al. NEJM 2000

Insulin vs. OHA

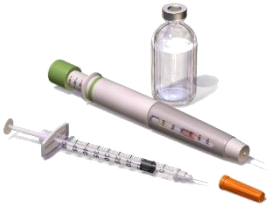
- **Meta-analysis of 6 RCTs comparing insulin vs. OHA** (glyburide & metformin)

  : No significant differences in glycemic control (fasting and postprandial glucose), adverse pregnancy outcomes (birth weight, large for gestational age, newborns and neonatal hypoglycemic events).

Dhulkotia JS et al. AJOG 2010

- Given the choice of insulin injection vs. tablets, women will opt for the latter

  : more convenient, cheaper, easier to administer and store, better compliance & adherence to the treatment



vs.


Postpartum surveillance

Postpartum management

- 50% likelihood developing overt DM within 20 years of delivery
- Recommendation: 75-g oral glucose tolerance test at 6 to 12 weeks after delivery
- F/U exam every 1-3 years
- Recurrence rate in subsequent pregnancy: 20-30%

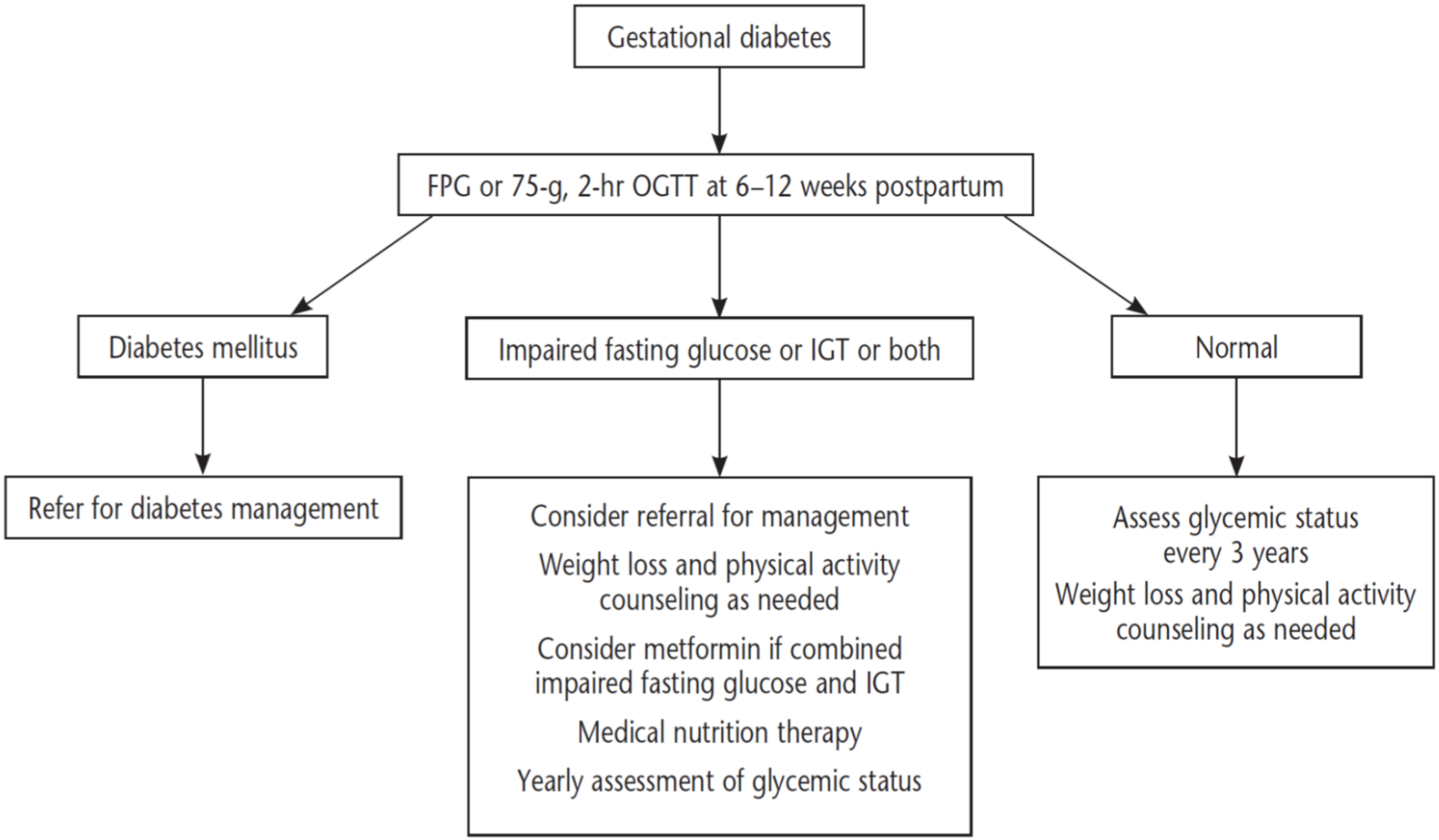
Table 2—*Metabolic assessments recommended after GDM*

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

*Classification of glucose metabolism by criteria recommended by the American Diabetes Association (8). OGTT, oral glucose tolerance test.

Fifth International Workshop-Conference on GDM DIABETES CARE, VOLUME 30, SUPPLEMENT 2, JULY 2007

Postpartum management



ACOG Practice Bulletin, Gestational Diabetes 2013

Postpartum management

ORIGINAL ARTICLE
Obstetrics & Gynecology

JKMS

http://dx.doi.org/10.3346/jkms.2015.30.12.1841 • J Korean Med Sci 2015; 30: 1841-1846

Postpartum Glucose Testing Rates Following Gestational Diabetes Mellitus and Factors Affecting Testing Non-compliance from Four Tertiary Centers in Korea

Geum Joon Cho,[1] Jung-Joo An,[2] Suk-Joo Choi,[2] Soo-young Oh,[2] Han-Sung Kwon,[3] Soon-Cheol Hong,[1] and Ja-Young Kwon[4]

[1]Department of Obstetrics and Gynecology, Korea University College of Medicine, Seoul; [2]Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [3]Department of Obstetrics and Gynecology, Konkuk University School of Medicine, Seoul; [4]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Yonsei University Health System, Seoul, Korea

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Accepted: 1 September 2015

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Ja-Young Kwon, MD
Department of Obstetrics and Gynecology, Yonsei University

The purpose of this study was to investigate postpartum glucose testing rates in patients with gestational diabetes mellitus (GDM) and to determine factors affecting testing non-compliance in the Korean population. This was a retrospective study of 1,686 patients with GDM from 4 tertiary centers in Korea and data were obtained from medical records. Postpartum glucose testing was conducted using a 2-hr 75-g oral glucose tolerance, fasting glucose, or hemoglobin A1C test. Test results were categorized as normal, pre-diabetic, and diabetic. The postpartum glucose testing rate was 44.9% (757/1,686 patients); and of 757 patients, 44.1% and 18.4% had pre-diabetes and diabetes, respectively. According to the multivariate analysis, patients with a high parity, larger weight gain during pregnancy, and referral from private clinics due to reasons other than GDM treatment were less likely to receive postpartum glucose testing. However, patients who had pharmacotherapy for GDM were more likely to be screened. In this study, 55.1% of patients with GDM failed to complete postpartum glucose testing. Considering the high prevalence of diabetes (18.4%) at postpartum, clinicians should emphasize the importance of postpartum diabetes screening to patients with factors affecting testing noncompliance.

Keywords: Diabetes, Gestational; Postpartum Glucose Screening; Referral

Postpartum management

- Retrospective study of 1,686 patients with GDM from 4 tertiary centers in Korea (삼성서울병원, 고대구로병원, 세브란스병원, 건국대병원), 2008-2011
- PP test: 75 g OGTT, FBS or HbA1C
- PP test rate: 44.9% (757/1,686)
- Results: Normal (37.5%)
  Pre-diabetes (44.1%)
  DM (18.4%)

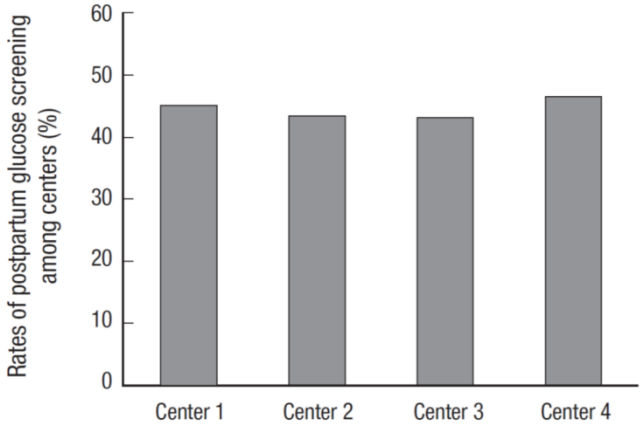

Fig. 1. The rates of postpartum glucose screening among 4 centers.

- Lower rate of PP test: high parity, larger weight gain during pregnancy, referral from private clinics due to reasons other than GDM
- Higher rate of PP test: pharmacotherapy for GDM

Postpartum management

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CLINICAL ARTICLE

A Korean multicenter study of prenatal risk factors for overt diabetes during the postpartum period after gestational diabetes mellitus

Na-Ri Shin [a], So-Yeon Yoon [a], Geum Joon Cho [b], Suk-Joo Choi [a], Han-Sung Kwon [c], Soon Cheol Hong [b], Ja-Young Kwon [d], Soo-young Oh [a,*]

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ABSTRACT

Objective: To identify prenatal risk factors for postpartum diabetes among pregnant women with gestational diabetes mellitus (GDM). *Methods:* In a retrospective study, baseline characteristics and data from a postpartum 75-g glucose tolerance test (GTT) were reviewed for patients with GDM who had delivered in four Korean tertiary institutions from 2006 to 2012. Clinical characteristics were compared between women with and those without postpartum diabetes. Cutoffs to predict postpartum diabetes and diagnostic values were calculated from receiver operating characteristic (ROC) curves. *Results:* Of 1637 patients with GDM, 498 (30.4%) underwent a postpartum 75-g GTT. Postpartum diabetes was diagnosed in 40 (8.0%) patients and impaired glucose intolerance in 157 (31.5%). Women with postpartum diabetes had higher glycated hemoglobin (HbA_{1c}) levels at GDM diagnosis ($P = 0.008$) and higher 100-g GTT values ($P < 0.05$ for all). In ROC curve analysis, optimal cutoffs for predicting postpartum diabetes were 0.058 for HbA_{1c} level and 5.3 mmol/L (fasting), 10.9 mmol/L (1 h), 10.2 mmol/L (2 h), and 8.6 mmol/L (3 h) for 100-g GTT. The highest sensitivity was observed for 3-h 100-g GTT (76.9%) and the highest positive predictive value was for HbA_{1c} at diagnosis (15.2%). *Conclusion:* HbA_{1c} level at GDM diagnosis and 100-g GTT values could be used to identify patients at high risk of postpartum diabetes who should undergo postpartum screening.

Postpartum management

- Retrospective study of 498 patients with GDM who underwent PP 75-g GTT from 4 tertiary centers in Korea, 2006-2012
- Postpartum diabetes 40 (8.0%), impaired glucose intolerance 157 (31.5%)
- Women with postpartum diabetes had higher HbA1c levels at GDM diagnosis (P=0.008) and higher 100-g GTT values (P<0.05 for all)

Table 2
Diagnostic performance of HbA_{1c} at diagnosis and 50-g and 100-g GTT values for prediction of overt diabetes in the postpartum period.

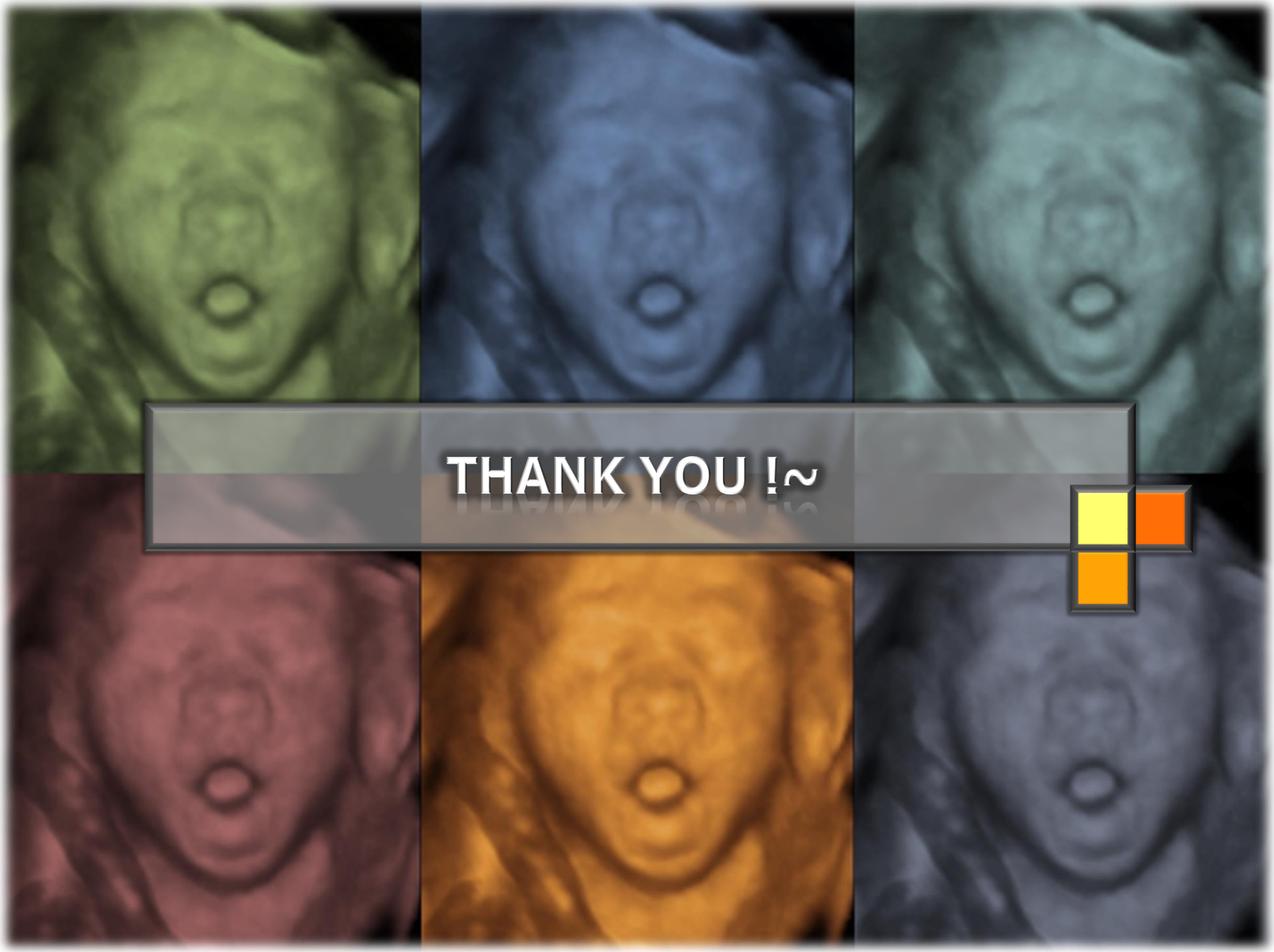
Risk factor	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
HbA_{1c} at diagnosis ≥0.058	63.6	72.0	15.2	96.2
50-g GTT ≥9.3 mmol/L	69.6	58.2	9.2	96.9
100-g GTT				
Fasting, ≥5.3 mmol/L	51.9	69.0	10.6	95.3
After 1 h, ≥10.9 mmol/L	70.4	59.1	10.9	96.6
After 2 h, ≥10.2 mmol/L	70.4	64.1	12.3	96.8
After 3 h, ≥8.6 mmol/L	76.9	65.5	13.4	97.6

Summary

- Increasing incidence of diabetes during pregnancy (both PGDM & GDM)
- Goal of glycemic control: minimize the complications (maternal, fetal & neonatal)
- SMBG is a essential component of therapy: FBS and either PP1 or PP2
- Maintain BSL as close to normal as possible, avoiding hypoglycemia
- Target BSL: FBS <95 mg/dL, PP1 <130-140 mg/dl, PP2 <120 mg/dl

Summary

- Diet & exercise ➔ pharmacological therapy
- Insulin, glyburide, and metformin are safe and effective therapies for GDM
  - Rapid-acting insulin combined with intermediate/long-acting insulin
  - The use of OHA in GDM is a safe alternative with similar or even improved outcomes compared to insulin
- Postpartum surveillance: 75-g oral GTT at 6 to 12 weeks after delivery


THANK YOU !~

Pharmacological treatment for GDM

- Insulin should be considered as the first-line treatment in women with GDM who are at high risk of failing on oral anti diabetic therapy, including some of the following factors:

  1) Diagnosis of diabetes <20 weeks of gestation
  2) Need for pharmacologic therapy >30 weeks
  3) Fasting plasma glucose levels >110 mg/dL
  4) 1-h postprandial glucose >140 mg/dL
  5) Pregnancy weight gain >12 kg

- The following insulins may be considered safe and effective treatment during pregnancy: regular insulin, NPH, Lispro, Aspart, and Detemir.

FIGO GDM Initiative's Recommendations for pharmacological treatment in women with GDM. IJGO 2015

Insulin vs. OHA

- **Meta-analysis**

1) Metformin vs. insulin: ↓ maternal weight gain, ↓ postprandial blood glucose, ↑ preterm birth, ↓ gestational age at delivery, ↓ pregnancy induced hypertension, ↓ severe neonatal hypoglycemia, failure rate of metformin 34 %

2) Glyburide vs. insulin: ↑ mean birth weight, ↑ macrosomia, ↑ neonatal hypoglycemia, no impact on gestational age at delivery

3) Metformin vs. glyburide: ↓ maternal weight gain, ↓ birth weight, ↓ macrosomia, ↓ large for gestational age.

Balsells M et al. BMJ 2015