제28차 대한당뇨병학회
춘계학술대회

8 May, 2015
광주 김대중 기념관

Medical Management of Diabetic Pregnancy

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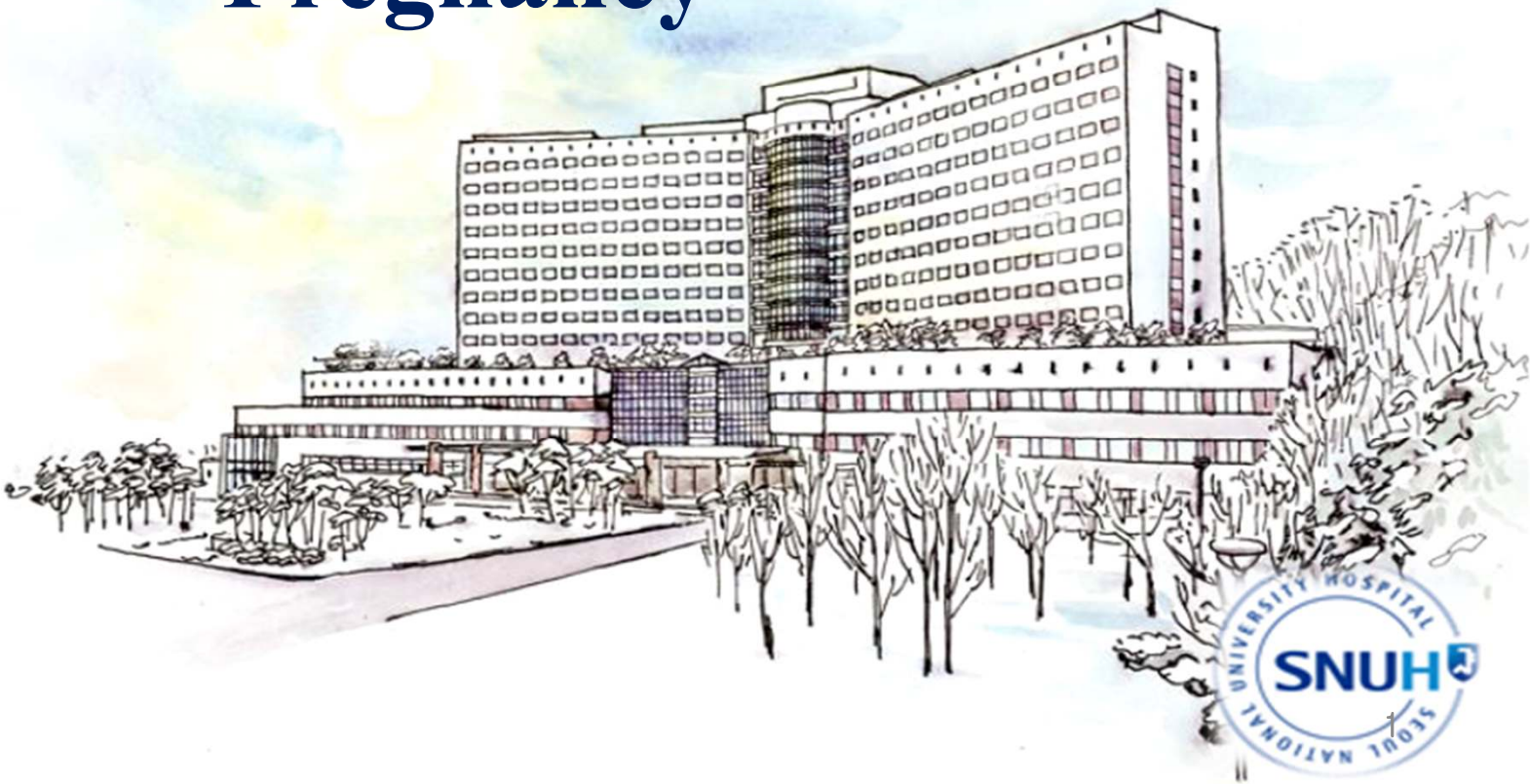


Invited Panelist

- 김문영 교수
  - 단국의대 제일병원 산부인과
  - 산과학, 임신성 당뇨병

- 홍준석 교수
  - 분당서울대학교병원 산부인과
  - 산과학, 모체태아의학

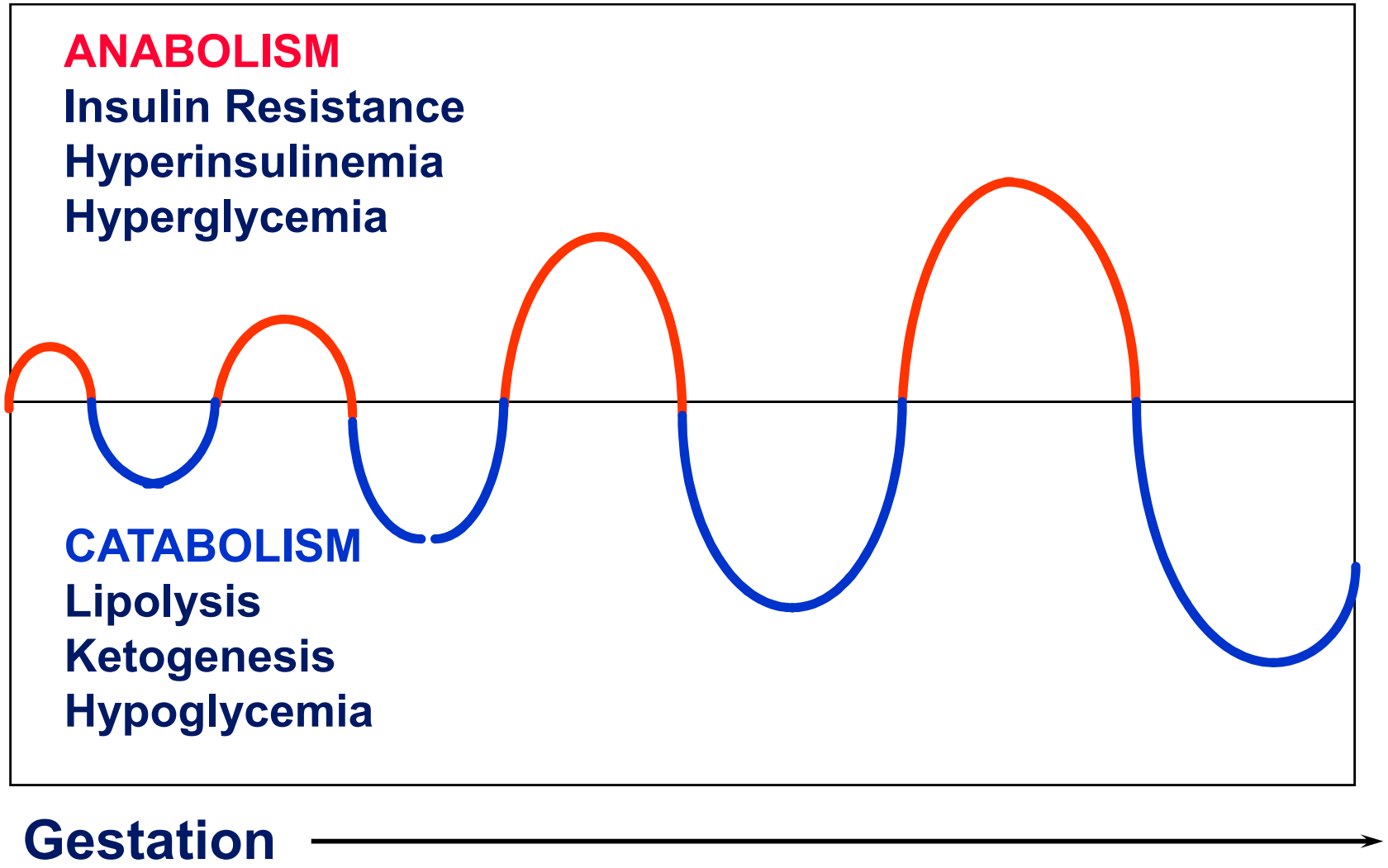
Contents

- Case Presentation & Discussion
  - Pregestational diabetes - T1DM
  - Drug treatment during pregnancy
  - Postpartum care
- Summary

당뇨병 임신의 분류 및 임상적 문제점

- 임신전 당뇨병 (Pregestational Diabetes, PGDM)
  - 당뇨병의 종류 (T1DM-DKA, T2DM- obesity, HTN)
  - 대사조절의 정도와 시기
    - 임신초기 (선천성 기형, 자연유산)
    - 임신후반기 (고인슐린혈증, 과다성장, 사산, 호흡곤란증)
  - 당뇨병성 만성합병증의 유무
    - 망막증 (임신 중 악화됨)
    - 신증 (부종, 고혈압, 태아발육부진)
    - 동맥경화증 (임신부의 사망)
- 임신성 당뇨병 (Gestational Diabetes Mellitus, GDM)
  - 태아의 위험 – diabetic fetopathy
  - 임산부의 위험- future T2DM, MetS, CVD
  - 대사조절 – insulin Tx

Metabolic Changes in Pregnancy



Early Problems in Diabetic Pregnancy

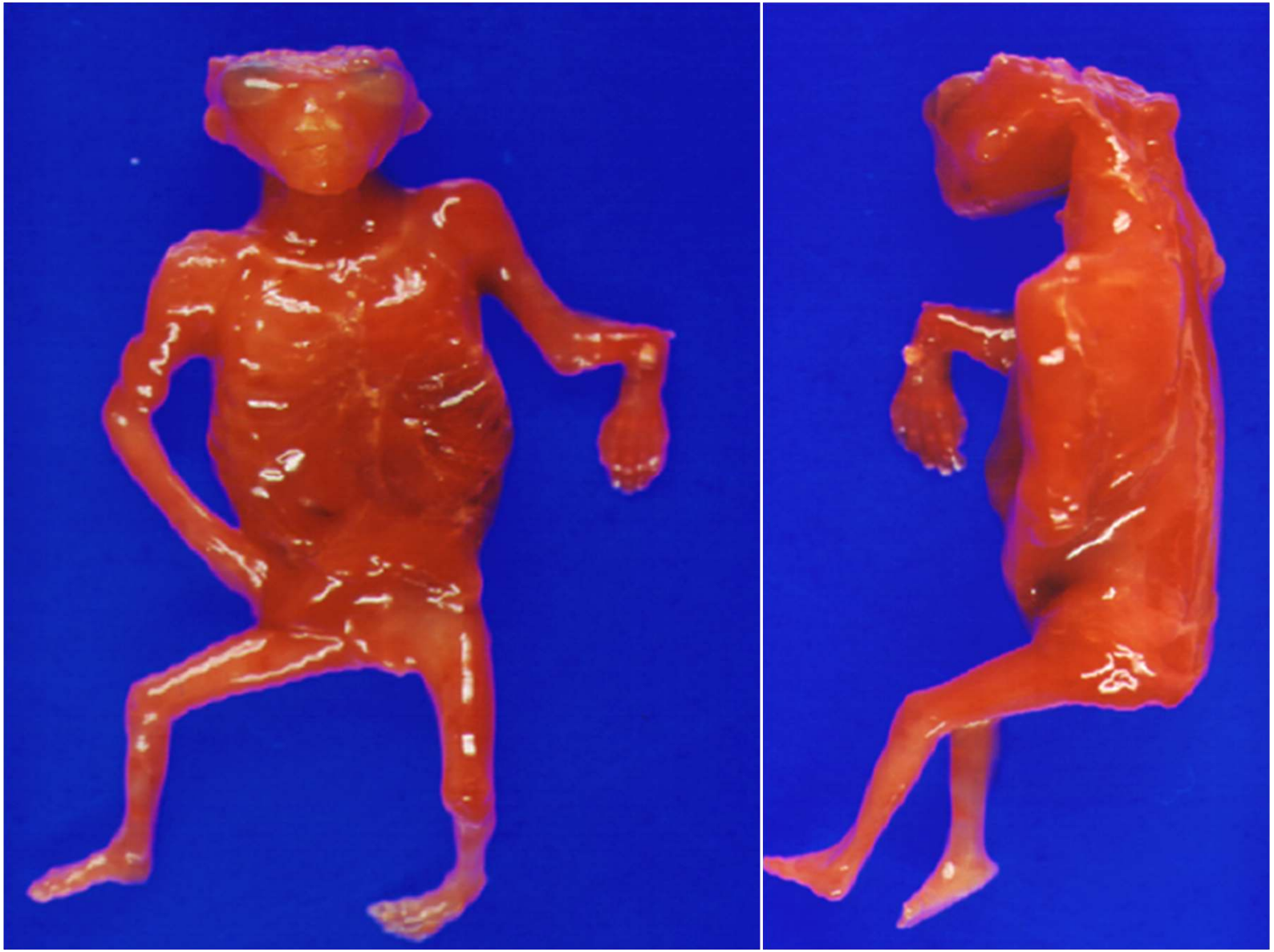
Congenital Anomaly

- Increased risk of congenital anomalies: 6-12%
- Congenital anomalies accounts for ~ 40% of the perinatal loss
- Cardiac, neural tube, or skeletal origin
- More commonly multiple, severe, and fatal

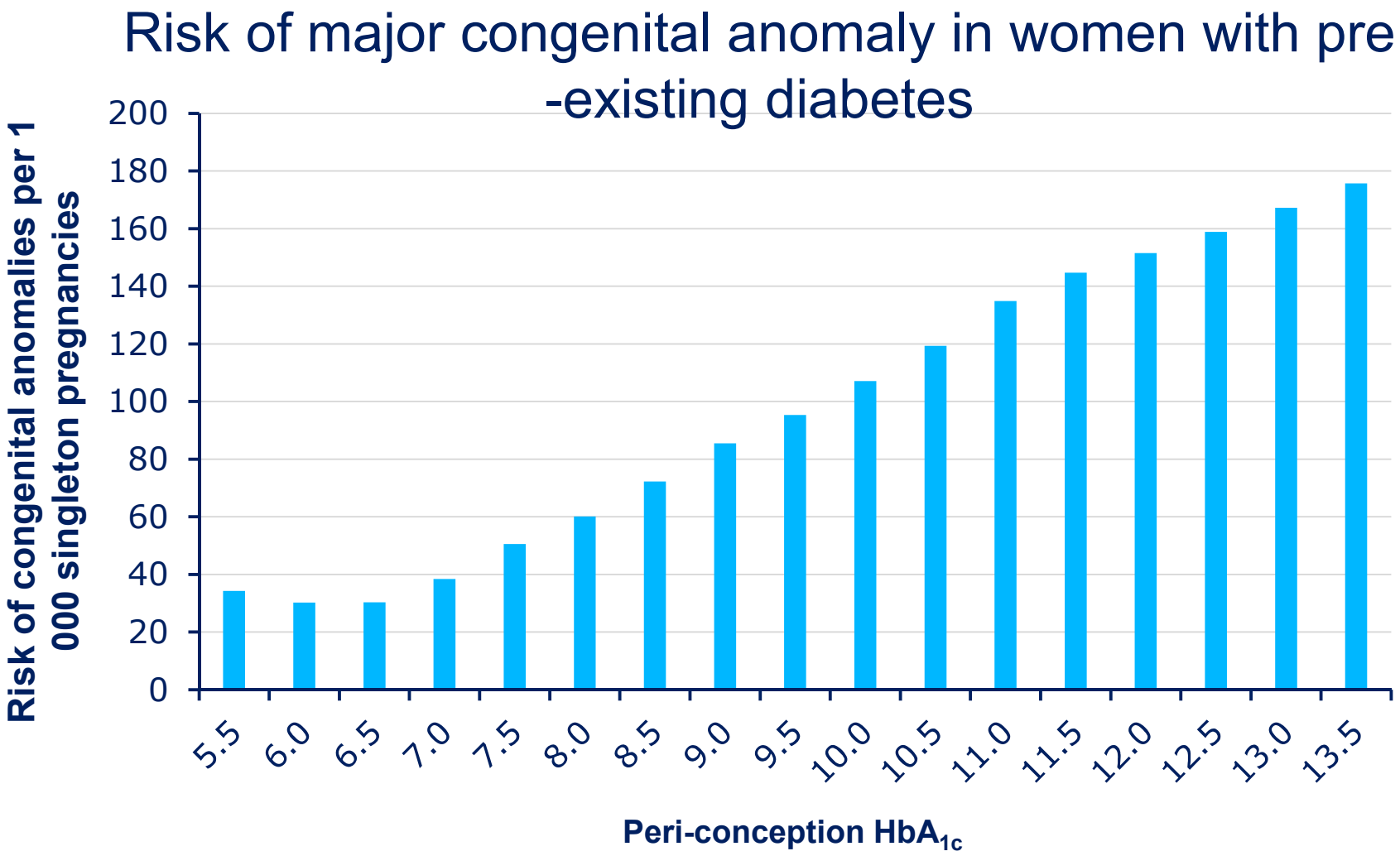
Spontaneous Abortion

- Incidence of SAB: unknown but reported as high as 30%, double that of the general population
- Related to maternal metabolic control

A Case of Anencephaly in Women with T2DM



Hyperglycaemia at conception associated with risk of congenital malformations



Bell *et al. Diabetologia* 2012;55:936–47

Congenital Anomalies and Pre-conception Care

	Pre-conception group		Registered already pregnant	
Author	Infants	Anomalies	Infants	Anomalies
Fuhrmann et al.	128	1 (0.8)	292	16 (5.5)
Fuhrmann et al.	56	1 (1.8)	144	6 (4.2)
Goldman et al.	44	0	31	2 (6.5)
Mills et al.	347	17 (4.9)	279	25 (9.0)
Damm et al.	283	7 (2.5)	148	15 (10.1)
Steel et al.	196	3 (1.5)	117	14 (12.0)
Kitzmiller	84	1 (1.2)	110	12 (10.9)
Rosenn et al.	28	0	71	1 (1.4)
Tchobroutsky et al.	40	0	186	16 (8.6)
Willhoite et al.	58	1 (1.7)	93	8 (8.6)
Total	**1264**	**31 (2.5)**	**1471**	**115 (7.8)**

Data are n or n(%).

Kitzmiller et al., Diabetes Care, 1996

Preconception planning is important

- Pregnancy planning is key
- Meta-analysis of preconception care and major congenital malformations in recipients and non-recipients (Ray *et al.* 2001)
  - Recipients: 2.1% vs. non-recipients: 6.5%
  - RR 0.36; 95% CI 0.22–0.59
- **Preconception care is recommended**
  - "Women with diabetes and childbearing potential should be educated about the need for good glucose control before pregnancy and should participate in effective family planning" (Kitzmiller *et al.* 2008)

Ray et al. QJM 2001;94:435–44;
Kitzmiller et al. Diabetes Care 2008;31:1060–79

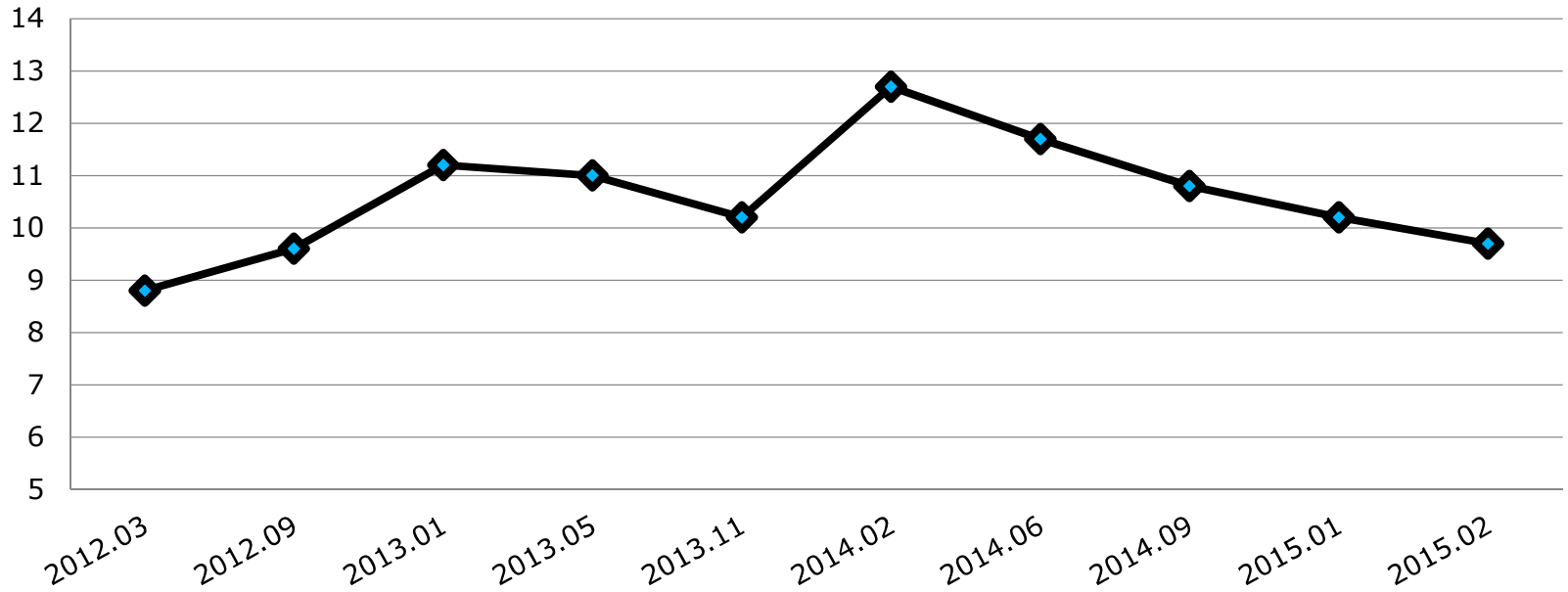
Case presentation (1)

- 30세 제1형 당뇨병 여성

- Present illness
  - 1990년 10월(만15세)에 처음 DKA가 발생하여 TI DM으로 진단받음. 현재 Lantus와 Humalog로 MSII regimen으로 혈당 조절 중.
  - 2014년 12월 결혼한 후 임신 되었고 임신 5주차 인근 산부인과에서 아기집이 작다고 들었고 9주차 검진 시에도 아기집에 1주정도 크기가 작다고 들었음.
  - 임신 후 혈당조절이 중요하다고 이야기를 들어, Lantus 11 U, Humalog는 탄수화물 양 계산하여 7~14 U로 주사함. 혈당 fluctuation이 심했다고 함. 연고지 관계상 산부인과, 안과, 내분비내과 진료 모두 한 병원에서 받기를 원하여 내원함.

- Para 0-0-0-0
- GA 10 wks
- EDC 2015-09-11
- 임신전 몸무게: 50 kg → 내원시 51.7 kg/ 신장 161 cm
- 당뇨병 가족력: 큰할머니
- SMBG fbs 140~216, pp2 67~247 mg/dL
- HbA1c 9.7% (2015.02.04)
- Complication w/u
    - Fd R) Macular hard exudate L) free (2015.02.04)
    - Microalb/Cr ratio 8 mg/g (2015.02.04)

당화혈색소의 변화



- Past medical history
  - T1DM as above
  - HBV carrier
- Social history
  - No smoking, alcohol

- Laboratory exam
  - CBC 6700-11.8-150k
  - T. protein 6.2 mg/dl, Alb 3.7 mg/dl
  - T. bil 0.3 mg/dl, AST/ALT 13/8 mg/dl, ALP 31 mg/dl
  - BUN/Cr 12/0.35 mg/dl, E’ 135-3.8-101-22, Ca/P 8.5/4.2 mg/dl
  - HbA1c 9.1%
  - Microalb/Cr ratio 7.57 mg/g
  - T3 112 ng/dl fT4 0.95 ng/dl TSH 3.13 uIU/ml
  - Ketone 87 (20~530)

Hospital course

- 산부인과 타과의뢰
  - OB-USG
    - G-sac(+) Y-sac(+) FP(+) FHT(+)
    - CRL (3.98cm/10+6wks)
    - BO free
  - 정상임신 상태

- 안과 타과의뢰
  - Fundus: mild NPDR
  - 조영검사는 출산 후 시행

Panelist 에게 질문

- 임신을 해서 내원한 경우, 산과에서는 어떤 work-up을 하나요?
  - Congenital anomaly에 관한 검사
- 임신초기 USG의 역할은?
- 당화혈색소가 높은 상황에서 초기 산과 진찰에서 정상임신으로 보이면 선천성기형은 걱정을 안해도 되나요?

Antenatal care for women with diabetes

- Discuss information, education and advice about how diabetes will affect the pregnancy, birth and early parenting.
- If the woman has been attending for preconception care and advice, continue to provide information, education and advice in relation to achieving optimal blood glucose control.
- If the woman has not attended for preconception care and advice, give information, education and advice for the first time, take a clinical history to establish the extent of diabetes-related complications (including neuropathy and vascular disease), and review medicines for diabetes and its complications.

http://pathways.nice.org.uk/pathways/diabetes-in-pregnancy

임신 전에 내원하였다면

- 임신 전 시행하여야 할 검사는?
- 임신전 당뇨병 상담의 내용은?
- 당뇨병 교육 - 환자의 가족(남편)을 교육에 참여시킬 것인가?
  - 당뇨병 임신의 이해
  - 저혈당

임신전 당뇨병 검진

- 본 환자에게 임신 이전 시행하여야 할 검사는 무엇인가?
  - 혈관합병증, 임신전 산과검진, 혈당의 조절
  - 심전도
  - 24시간 소변검사(Ccr, protein), 신장기능, 감염
  - 안과검진(전문의)
  - 산부인과 진찰: rubella, 임신 가능성
  - 당화혈색소

임신전 당뇨병 상담

- 임신전 상담에는 어떤 내용을 포함해야 하는가?
  - 당뇨병 합병증의 영향; 인슐린 요구량; 저혈당 및 케톤산증
  - 임신; 선천성 기형 및 자연유산; 산과 합병증
  - 성장장애; 자녀의 당뇨병 발생
  - 혈당조절의 목표; 영양상담; 적극적인 인슐린 치료; 자가혈당측정법
  - 적절한 피임법과 계획임신

Recommended glycaemic control targets are more strict than for regular diabetes patients

Recommended that women monitor pre- and 1 or 2 h post-meals and at bedtime; occasional sample during night	
Preprandial glucose	60–99 mg/dL (3.3–5.4 mmol/L)
Peak postprandial glucose	100–129 mg/dL (5.4–7.1 mmol/L)
HbA_{1c}	<6.0%

"Before pregnancy, in order to prevent spontaneous abortions and major congenital m alformations, target HbA_{1c} is as close to normal as possible without significant hypogly caemia"

ADA. *Diabetes Care* 2010;33(Suppl. 1):S11–61;
Kitzmiller *et al. Diabetes Care* 2008;31:1060–79

Glycemic control targets by NICE

- Target blood glucose levels
  - fasting: < 95 mg/dL (5.3 mmol/L) and
  - 1 hour after meals: 140 mg/dL (7.8 mmol/L) or
  - 2 hours after meals: 115 mg/dL (6.4 mmol/L).
- HbA1c
  - Measure HbA1c levels in all pregnant women with diabetes at the booking appointment to determine the level of risk for the pregnancy.
  - Be aware that level of risk for the pregnancy for women with diabetes increases with an HbA1c level above 6.5%.
  - Measure HbA1c levels in all women with gestational diabetes at the time of diagnosis to identify those who may have pre-existing type 2 diabetes.
  - **Do not use** HbA1c levels routinely to assess a woman's blood glucose control in the second and third trimesters of pregnancy.

Case presentation (2)

- 30세의 임신부 (임신 30주)
- 인근병원에서 초음파상 거대아가 의심되어 내원
- 두 번째 임신으로 2년 전 첫 임신 때 임신성 당뇨병 진단.
- 임신 38 주에 4.4 kg의 사산아(남아)를 분만
- 가족력: 어머니 (45세); 제2형 당뇨병
- 신장 158 cm / 임신전 체중 65 kg (BMI, 26)– 현재 체중 72 kg

임신성 당뇨병 증례

- **100 g OGTT**

시간	공복	1	2	3
혈장 포도당 (mg/dL)	112	250	224	190

- **당화혈색소: 6.7%**
- **식사: GDM diet 1800 kcal**
- **Insulin Treatment: premixed insulin x 2/day**
- **GDM education: SMBG; Urine Ketone**

청중에게 질문

- 본 임신부에서 알아야 할 병력은 무엇인가요?

- 본 임신부가 임신 30^{+1}주가 아닌 임신 8주에 왔다면 어떤 검사가 필요할까요?

청중에게 질문

- 본 임신부에서 알아야 할 병력은 무엇인가?
  - **분만 후 경구당부하검사 여부**
  - **사산과 관련된 병력**

- 본 임신부가 임신 30^{+1}주가 아닌 임신 8주에 왔다면 어떤 검사가 필요할까요?

Panelist 에게 질문

- 임신 말기에 사산이 되는 경우, 일반적으로 어떤 원인이 있을까요?
- 산과적으로 사산을 예방하거나 예측할 수 있는 방법이 있을까요?
- 임신성 당뇨병 임신부에서 임신 말기에 사산이 되었다면 어떤 원인으로 사산이 되었을까요?

청중에게 질문

- 본 임신부가 임신 30^{+1}주가 아닌 임신 8주에 왔다면 어떤 검사가 필요할까요?

  - **당뇨병의 선별검사**
  - **초음파**

Panelist 에게 질문

- 임신성 당뇨병 진단 및 관리에 당화혈색소 검사가 도움이 될까요?
- 최근 임신부에서 비타민 D 혈중 농도를 많이 검사하는데, 임신성 당뇨병 임신부에서 도움이 될까요?
- 본 임신부에서 산전관리는 어떻게 진행하게 되나요?

청중에게 질문

- 임신성 당뇨병 임신부에서 언제 인슐린치료를 시작해야 하나요?
- 경구혈당강하제가 도움이 될까요?
- 탄수화물제한 식이가 도움이 될까요?

Diurnal Glycemic Profile by CGMS

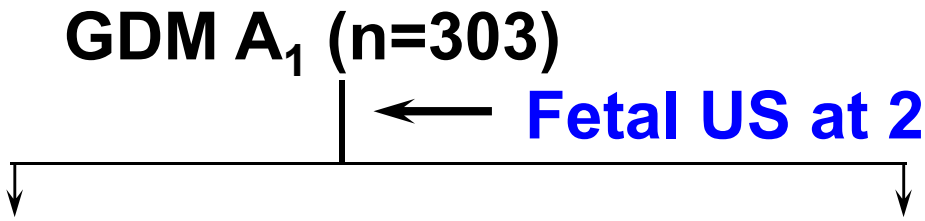
Variable	Women who were not obese (n = 42)	Obese women (n = 15)
Body mass index (kg/m^2)*	23.7 ± 1.8	31.2 ± 1.9
Gestational age at evaluation (wk)*	28.9 ± 8.1	30.1 ± 8.3
Glucose measurements per patient in 72 hours (n)*	746 ± 77	796 ± 63
Mean blood glucose level (mg/dL)*	83.6 ± 18	84.2 ± 16
Fasting glucose level (mg/dL)*	72.1 ± 13	73.2 ± 9
Analyzed meals (n)	378	135
Preprandial glucose level (mg/dL)*	81.2 ± 14	90.3 ± 19
Postprandial peak glucose value (mg/dL)*	106.2 ± 16	117.6 ± 8
Postprandial peak time (min)*	71.4 ± 30	88.0 ± 31
1-hour postprandial glucose value (mg/dL)*	103.2 ± 13	112.1 ± 13
2-hour postprandial glucose value (mg/dL)*	96.8 ± 12	107.4 ± 14
3-hour postprandial glucose value (mg/dL)*	85.9 ± 17	102 ± 16

AJOG 2004; 191:949-53

Insulin Treatment in GDM

- When appropriate MNT does not consistently maintain fasting (≤95mg/dL) or 2-h postprandial plasma glucose (≤120 mg/dL).
- To prevent macrosomia, insulin should be started when fasting is >90mg/dL and/or 1-h postprandial plasma glucose is >120 mg/dL.
- If fetal abdominal circumference is >75th percentile ?

Fetal Ultrasound for Metabolic Therapy in Women with Mild GDM



	S. Diet (n=171)	S. Diet (n=24)	R. Diet (n=29)	R. Insulin (n=30)
GA delivery (wk)	39.6±0.1	39.0±0.3	39.5±0.2	39.6±0.2
Birth weight (g)	3444±38	3804±92*	3878±72*	3647±67
LGA (%)	24(14%)	9(38%)*	13(45%)*	4(13%)

* P<0.01 vs. group with fetal AC< 75th

Buchanan et al., Diabetes Care, 1993

NICE recommendation

- Women with diabetes may be advised to use metformin as an adjunct or alternative to insulin in the preconception period and during pregnancy, when the likely benefits from improved blood glucose control outweigh the potential for harm.
- All other oral blood glucose-lowering agents should be discontinued before pregnancy and insulin substituted.
- Be aware that data from clinical trials and other sources do not suggest that the rapid-acting insulin analogues (aspart and lispro) adversely affect the pregnancy or the health of the fetus or newborn baby.
- Consider continuing treatment with long-acting insulin analogues (insulin detemir or insulin glargine) in women with diabetes who have established good blood glucose control before pregnancy.

Low-Carbohydrate Diet for the treatment of gestational diabetes mellitus

- Treatment of women with GDM using a low-CHO diet did not reduce the number of women needing insulin and produced similar pregnancy outcomes.(Diabetes Care 36:2233–2238, 2013)
- Compared with a conventional, lower-carbohydrate/HF diet (40% carbohydrate/45% fat/15% protein), consumption of a higher-complex carbohydrate (HCC)/lower-fat (LF) Choosing Healthy Options in Carbohydrate Energy (CHOICE) diet (60/25/15%) would result in 24-h glucose area under the curve (AUC) profiles within therapeutic targets and lower postprandial lipids. (Diabetes Care 2014;37:1254–1262)

Case presentation (3)

- 31세의 임신부
- 임신 27주에 임신성 당뇨병으로 진단.
- 임신성 당뇨병 식이 1900 Kcal와 인슐린으로 혈당을 조절.
- 임신 39주에 자연분만으로 3.5 kg의 남아를 분만
- 신장 163 cm 임신전 체중 56 kg (BMI, 21)– 분만시 체중 65 kg
- 분만 후 모유 수유 중
- 분만 2달 후 75 g OGTT, 60 kg
  - 93 (fasting)-182 (30 min)-211 (60 min)-194 (90 min)-172 (120 min)

Panelist 에게 질문

- 본 임신부가 분만 후 퇴원 시에 어떤 교육이 필요할까요?

임신성 당뇨병의 분만 후 관리

- 분만 후 어떤 정보를 줄 것인가?
  - **경구당부하검사**
  - **모유 수유시 적절한 식이조절 - 체중 감소**
  - **매년 혈당 검사, 당뇨병의 증상**
  - **아이를 더 원할 경우, 임신 전 당뇨병 여부 확인**

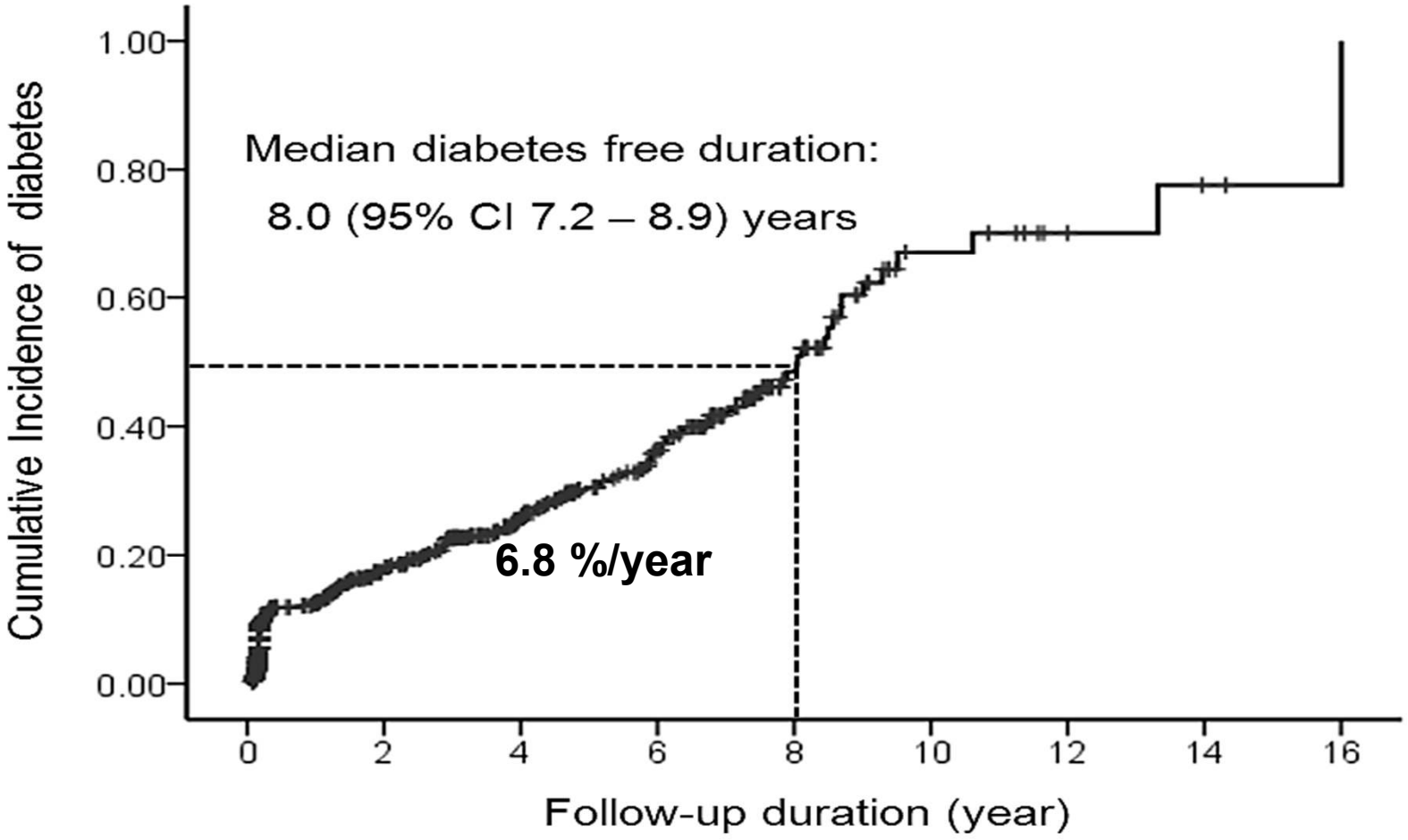
청중에게 질문

- 75 g OGTT 시에 어떤 지표가 당뇨병 발생 예측에 도움이 될까요?

- 만약 1년 후에 임신을 계획한다면 임신성 당뇨병이 재발할 확률은 어느 정도 일까요?

Clinical and Genetic Risk Factors for Type 2 Diabetes at Early or Late Post Partum After GDM

Cumulative Incidence of T2DM after GDM in Korean women



J Clin Endocrinol Metab 98: E744–E752, 2013

Table 4. Independent Risk Factors for T2DM Early or Late Post Partum According to Multivariate Logistic Regression Analysis[a]

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
T2DM at 2 mo post partum (early converters)						
Prepregnancy BMI	1.08 (1.01–1.16)	**.028**	1.08 (1.00–1.17)	.051	1.09 (1.00–1.18)	.045
Gestational week at diagnosis	0.95 (0.90–1.01)	.092	0.93 (0.86–1.00)	**.047**	0.93 (0.86–1.00)	**.048**
Insulin treatment	1.71 (0.81–3.60)	.159	1.97 (0.83–4.70)	.126	2.06 (0.87–4.87)	.101
Fasting glucose	0.98 (0.96–1.01)	.142	0.98 (0.96–1.01)	.308	0.99 (0.96–1.01)	.317
AUC of glucose	1.01 (1.00–1.01)	**.006**	1.01 (1.00–1.01)	.060	1.01 (1.00–1.01)	.076
Log fasting insulin	0.04 (0.00–0.38)	**.006**	0.05 (0.00–0.89)	**.041**	0.04 (0.00–0.71)	**.028**
Log AUC of insulin	1.40 (0.16–12.47)	.765	1.00 (0.07–13.91)	1.000	1.34 (0.10–18.57)	.825
IS/IR disposition index	0.10 (0.02–0.49)	**.005**	0.15 (0.02–0.99)	**.049**	0.13 (0.02–0.87)	**.036**
rs10811661 (*CDKN2A/2B*)			1.18 (0.76–1.84)	.462		
rs1111875 (*HHEX*)					1.44 (0.93–2.23)	.106
T2DM at more than 1 y of follow-up (late converters)						
Prepregnancy BMI	1.11 (1.02–1.20)	**.013**	1.08 (0.98–1.19)	.114		
Insulin treatment	0.92 (0.40–2.14)	.849	0.76 (0.30–1.92)	.558		
Fasting glucose	1.01 (0.98–1.04)	.622	1.01 (0.97–1.04)	.665		
AUC of glucose	1.01 (1.00–1.01)	**.013**	1.01 (1.00–1.01)	.082		
Log AUC of insulin	0.48 (0.14–1.71)	.260	0.73 (0.17–3.26)	.685		
IS/IR disposition index	0.61 (0.22–1.66)	.329	0.25 (0.06–0.99)	**.049**		
rs7754840 (*CDKAL1*)			1.39 (0.89–2.18)	.147		

Abbreviation: OR, odds ratio.

Subsequent pregnancy after GDM in Korean women

- The frequency of recurrent GDM in subsequent pregnancies was 45.0%.
- Women with IFG and/or IGT 2 months postpartum were at increased risk for recurrent GDM (RR 2.31, 95% CI 1.24–4.30).
- Higher BMI before the subsequent pregnancy, higher fasting glucose concentration 2 months postpartum, and lower 1-h insulin concentration of the diagnostic OGTT in the index pregnancy were independent risk factors for recurrence of GDM in subsequent pregnancies.

Diabetes Care 31:1867–1871, 2008

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