Pregnancy and Diabetes

Diabetes Symposium, 2019

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Conflicts

I have no relevant disclosures or conflict of interest with the material I'm presenting today.

Objectives

- Explain diabetes management in pregnancy.
- Describe the metabolism of normal pregnancy and the alterations that occur in overt and gestational diabetes.
- Describe the diagnostic criteria and screening recommended by the ADA.
- Describe potential maternal and fetal complications.
- Summarize treatment options in GDM.

Diabetes and Pregnancy

- Preconception
  - Effects of diabetes on maternal/fetal outcomes
    - Glycemic Control
    - Diabetes self-care
    - Comorbidities
    - Congenital Malformations
    - Macrosomia
    - Stillbirth
  - Effects of medications on outcomes

Risk factors for pregestational DM II

- Prepregnancy BMI >25 and at least one of the following (ADA 2017 guidelines):
  - Prior history of GDM
  - Prior infant weighing >4000g at birth
  - Chronic hypertension or cardiovascular disease
  - PCOS
  - Non-caucasian race
  - First degree relative with DM
  - A1C $\geq$ 5.7%
  - Hypercholesterolemia
  - Age >45
  - Physical inactivity

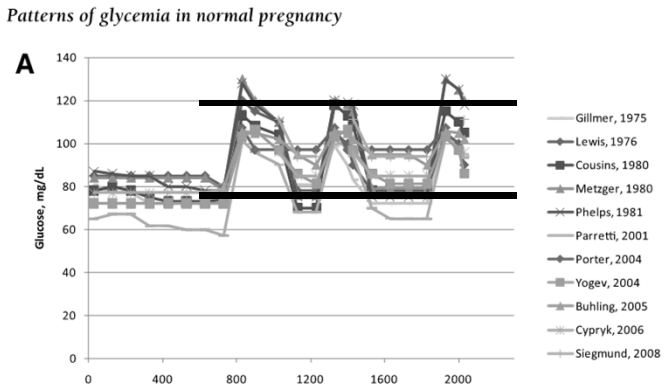
First trimester screening for women at risk for DM II

- American Diabetic Association Criteria for 2017 :
  - A1C $\geq$ 6.5%
  - Fasting glucose of $\geq$ 126mg/dl
  - Random glucose $\geq$ 200 mg/dl and hyperglycemia symptoms
  - 2 hour glucose tolerance test (GTT)
    - 75g glucose load
    - 2 hour glucose $\geq$ 200 mg/dl
- 1 hour screening GTT followed by 3 hour diagnostic GTT
- *If a patient passes early GTT, it still must be repeated at 24-28 weeks*

Glucose Thresholds & Complications

NORMOGLYCEMIA OF PREGNANCY

Glycemia in Normal Pregnancy



Hernandez. Diabetes Care. 2011

Glycemic Patterns

Median Results	
Fasting	71
1 hr	109
2 hr	99
24 hr	88

135 average = 2 SD above

Recommended	
1 hr	< 122
2 hr	< 110

140

120

Diabetes During Pregnancy

MATERNAL COMPLICATIONS

Maternal Complications- Diabetes

Table 4
UK Confidential Enquiry into Maternal and Child Health (CEMACH) Survey. Pregnancy in women with type 1 and type 2 diabetes in England, Wales and Northern Ireland, 2002–2003.[1]

	IDDM	UK	Rate Ratio
Birth weight > 90th percentile	52%	10%	5.2
Shoulder dystocia	7.9%	3%	2.6
Erb's Palsy	4.5/1000	0.42/1000	11
Preterm Delivery	37%	7.3%	5
Caesarean Section	67%	24%	2.8
Congenital Malformations	5.5%	2.1%	2.6
Neonatal Death	9.3/1000	3.6/1000	2.6
Perinatal Mortality	31.8/1000	8.5/1000	3.7

IDDM (baby of mothers with pregestational diabetes mellitus); UK (rate for general UK population). Perinatal mortality: fetal death between 24 weeks and one week after delivery

McCance, Best Practice & Research Clinical Endocrinology & Metabolism, 2011

Diabetic Ketoacidosis

Study	Time Interval	n	Incidence (%)	Fetal loss (%)
Lufkin, et al	1950-1979	228	7.9%	?
Cousins, et al	1965-1985	1508	9.3%	?
Kilvert, et al	1971-1990	635	1.7%	14% (2-3rd tri)
Rogers and Rogers	1980-1990	~3000	1%	?
Cullen, et al	1985-1995	520	2%	9%
Schneider, et al	1991-2001	2025	1.2%	27%

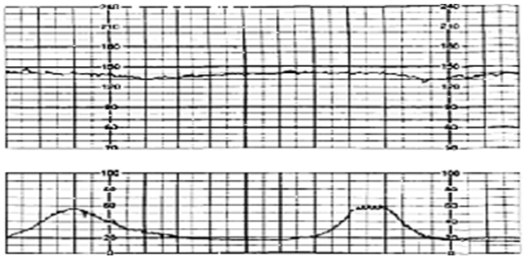
How pregnancy affects the disease

- Accelerated starvation
- Insulin antagonistic state
- Lowered buffering capacity
  - pH 7.4/PCo2 30mm Hg/Bicarb 20 mEq/L.
- Emesis
- Infection

Can lower threshold

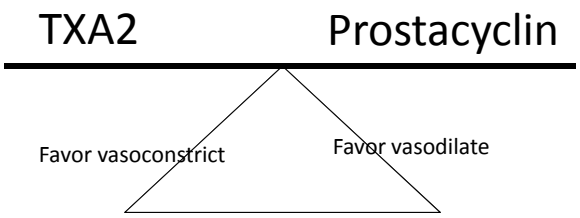
How the disease affects pregnancy

- Fetal Loss (9-27%)

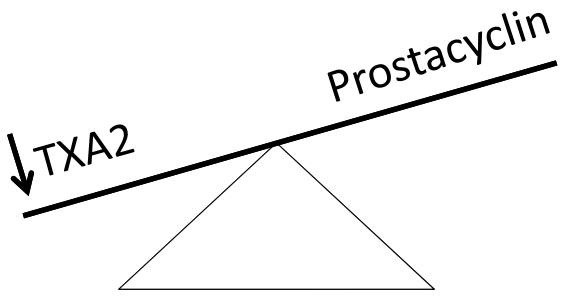


Creasy (p963, 6th ed) "…even when fetal status is questionable during the phase of therapeutic volume and plasma glucose correction, emergency cesarean section should be avoided"

Aspirin



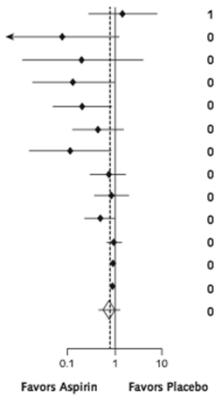
Aspirin



LDA inhibits TXA2 > Prostacyclin production = vasodilate

Figure 3. **Pooled analysis of preeclampsia from trials of women at risk for preeclampsia, sorted by sample size.**

Study, Year (Reference)	PE Incidence (Placebo), %	Dose, *mg*	RR (95% CI)	Events/Total, *n/N*		Weight, % *
				Aspirin	Placebo	
Grab et al, 2000 (57)	10	100	1.43 (0.27–7.73)	3/22	2/21	1.52
Wallenburg et al, 1986 (54)	30	60	0.07 (0.00–1.20)	0/21	7/23	0.57
Caspi et al, 1994 (56)	9	100	0.19 (0.01–3.80)	0/24	2/23	0.50
Schiff et al, 1989 (47)	23	100	0.13 (0.02–1.00)	1/34	7/31	1.05
Vainio et al, 2002 (41)	23	49	0.20 (0.05–0.86)	2/43	10/43	2.00
Hermida et al, 1997 (39)	14	100	0.43 (0.12–1.56)	3/50	7/50	2.49
McParland et al, 1990 (49)	19	75	0.11 (0.01–0.81)	1/48	10/52	1.07
Villa et al, 2013 (50)	18	100	0.72 (0.31–1.65)	8/61	11/60	5.38
Viinikka et al, 1993 (58)	11	50	0.84 (0.37–1.95)	9/97	11/100	5.41
Ayala et al, 2013 (55)	13	100	0.49 (0.25–0.99)	11/176	22/174	7.32
Yu et al, 2003 (46)	19	150	0.95 (0.67–1.35)	49/276	52/278	17.26
MFMU, 1998 (44)	20	60	0.90 (0.77–1.06)	226/1254	250/1249	27.63
CLASP, 1994 (53)	8	60	0.88 (0.75–1.03)	267/3992	302/3982	27.80
Overall (I^2 = 40.5%; P = 0.064)			0.76 (0.62–0.95)	580/6098	693/6086	100.00
With estimated predictive interval			(0.47–1.24)			

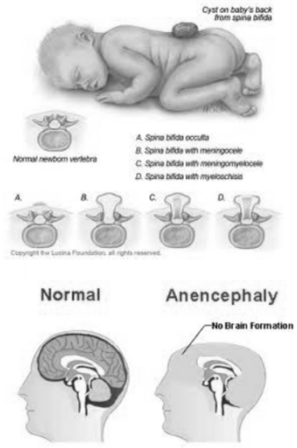


Henderson, Ann Int Med 2014

FETAL COMPLICATIONS

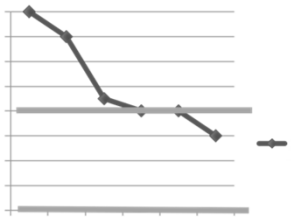
Congenital Anomalies

- Sacral Agenesis
- Spina Bifida
- Anencephaly
- Heart Defects



Fetal Complications

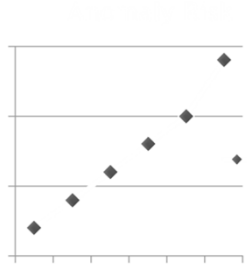
Glucose Thresholds



Fetal Complications

Anomalies	140
Fetal Death	110
Respiratory Dis	110
Macrosomia	100
Growth Restriction	
Hypoglycemia	

Anomalies



	Anomaly Risk
Non-diabetic	2%
HbA1c 7%	3%
HbA1c 9%	6%
HbA1c 11%	10%

Guerin. Diabetes Care. 2007

STILLBIRTH

	Age	Years of DM	Smoke	Pre HbA1c	Early HbA1c	Late HbA1c	EGA
Stillbirth	27	11 yrs	64%	7.9%	7.9%	8.0%	35 wks
Reference	30	14 yrs	29%	7.4%	7.0%	6.3%	37 wks

Women who experienced stillbirth were characterized by a high incidence of suboptimal glycemic control, diabetic nephropathy, smoking and low socioeconomic status.

Respiratory Distress

Etiologies:

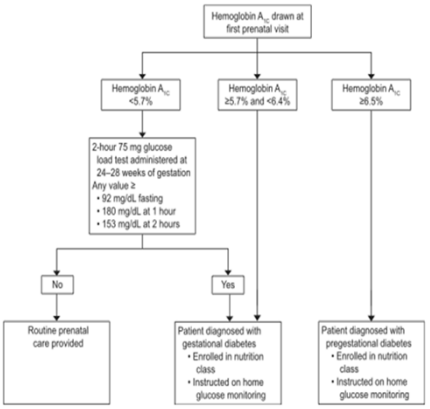
1. Increased premature delivery
2. Hyperglycemia and Hyperinsulinemia delay glucocorticoid production and lung maturation

The risk of RDS among preterm infants of well-controlled diabetic mothers approaches that of infants born to non-diabetic mothers at similar gestational ages.

GESTATIONAL DIABETES

Gestational Diabetes Screening

The International Association of the Diabetes and Pregnancy Study Groups Compared With Carpenter-Coustan Screening

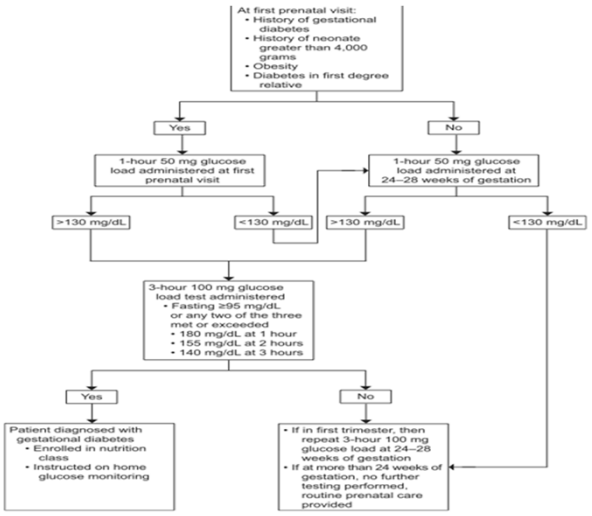


- n=6,066
  - 2,972 (standard)
  - 3,095 (protocol)
- Rate of GDM
  - Standard 17%
  - Protocol 27%

p <0.001

Feldman et al, Obstet Gynecol 2016

Diagnosis of GDM



Diagnosis of GDM

Table 3. Unadjusted and Adjusted Odds Ratios With the Before Group as the Referent Group

Pregnancy Outcomes, Before vs After	OR (95% CI)	Adjusted OR (95% CI)
LGA	0.9 (0.76–1.07)	0.84 (0.68–1.03)
Macrosomia	0.83 (0.69–1)	0.81 (0.65–1.01)
NICU admissions	1.37 (1.08–1.74)*	1.24 (0.94–1.65)
Preterm births	1.08 (0.89–1.3)	1.03 (0.82–1.3)
Total cesarean deliveries	1.27 (1.13–1.42)†	1.22 (1.06–1.4)*
Primary cesarean deliveries	1.3 (1.13–1.5)‡	1.2 (1.01–1.42)§
Cesarean deliveries as a result of arrest disorders	1.27 (1.06–1.52)	1.12 (0.9–1.39)
Preeclampsia	1.47 (1.12–1.93)*	1.73 (0.87–3.51)
Hyperbilirubinemia	1.16 (0.98–1.38)‖	1.13 (0.92–1.38)
Shoulder dystocia	0.64 (0.25–1.55)	0.69 (0.25–1.76)

OR, odds ratio; CI, confidence interval; LGA, large for gestational age; NICU, neonatal intensive care unit.
Adjusted odds ratios account for maternal age, race–ethnicity, parity, prenatal body mass index measured at first prenatal care visit, and hypertension status.

Table 4. Unadjusted and Adjusted Odds Ratios for Events by Body Mass Index at First Prenatal Care Visit

Pregnancy Outcomes, Before vs After	OR (95% CI)	Adjusted OR (95% CI)
LGA	1.08 (1.06–1.09)*	1.07 (1.06–1.09)*
Macrosomia	1.07 (1.05–1.09)*	1.06 (1.04–1.08)*
NICU admissions	1.01 (0.99–1.03)	0.99 (0.97–1.02)
Preterm births	1.04 (1.02–1.05)*	1.02 (1–1.03)
Total cesarean deliveries	1.05 (1.03–1.06)*	1.04 (1.03–1.05)*
Primary cesarean deliveries§	1.03 (1.02–1.05)*	1.03 (1.02–1.05)†
Cesarean deliveries as a result of arrest disorders	1.02 (1.01–1.04)‡	1.03 (1.01–1.05)‡
Preeclampsia	1.07 (1.04–1.09)*	0.97 (0.93–1.01)
Hyperbilirubinemia	1.01 (0.99–1.03)	1.01 (0.99–1.03)
Shoulder dystocia	1.08 (1.02–1.15)‡	1.06 (0.99–1.13)*

OR, odds ratio; CI, confidence interval; LGA, large for gestational age; NICU, neonatal intensive care unit.
Adjusted odds ratios account for maternal age, race–ethnicity, parity, and hypertension status. Body mass index was treated as a continuous variable.

Feldman et al, Obstet Gynecol 2016

Incidence

- 3.5-12% in pregnancy
- 30-50% recurrence risk
- 7x increase risk developing DM2

Risks Associated with GDM

- Maternal
  - Preeclampsia
  - C-section
  - Type II DM
- Neonatal
  - Birth weight >4000g
  - Shoulder dystocia
  - Hypoglycemia
  - Stillbirth
  - Increased risk of childhood obesity

Maternal Complications

Gestational

- Gestational HTN/Preeclampsia
- LGA infant
- Traumatic vaginal delivery
- Cesarean delivery
- Type 2 DM

Pre-Gestational

- Gestational HTN/Preeclampsia
- SGA or LGA
- Cesarean delivery
- Worsening end-organ disease
  - Eyes, Kidneys

Management

- Dietary Modification
  - CDE
- Monitoring of Blood Glucose
- Medication
- Other
  - Exercise
    - Blood Glucose ☑
    - Insulin requirements ☒

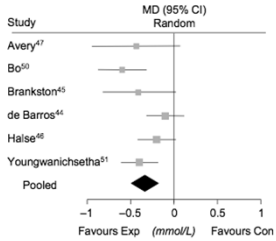


Figure 4. Mean difference (95% CI) in effect of exercise plus usual care versus usual care only on postprandial blood glucose (mmol/L) in women with gestational diabetes mellitus, in a sensitivity analysis excluding the study by Jovanovic-Peterson et al[49] due to heterogeneity.

Harrison, et al JPHYS, 2016

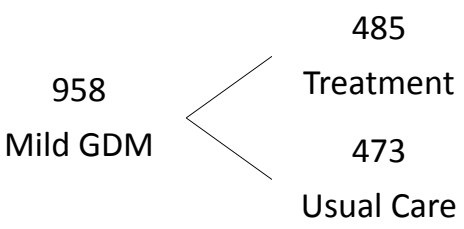
GDM Diagnostic Options (24-28 weeks)

- **<u>Two step</u>:**
  - 50g glucose load
    - Glucose threshold of 135 or 140 mg/dl
    - Consider diagnostic if ≥ 200 mg/dl
  - 100g glucose load (one or two abnormal values)
    - Fasting >95
    - 1 hr >180
    - 2 hr >155
    - 3 hr > 140
- **<u>One step</u>:**
  - 75g glucose load (one abnormal value)
    - Fasting ≥ 92
    - 1hr ≥ 180
    - 2hr ≥ 153

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes



Landon. 2009

Treatment of Mild GDM

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

Landon. NEJM. 2009

Treatment of Mild GDM

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

Landon. NEJM. 2009

Am J Obstet Gynecol. 2016 Sep;215(3):287-97. doi: 10.1016/j.ajog.2016.04.040. Epub 2016 Apr 29.

Single abnormal value on 3-hour oral glucose tolerance test during pregnancy is associated with adverse maternal and neonatal outcomes: a systematic review and metaanalysis.

Roeckner JT[1], Sanchez-Ramos L[2], Jijon-Knupp R[3], Kaunitz AM[3].

- 2016 metaanalysis of 25 studies with 4466 women total
- Women with 1 abnormal on 3 hour GTT vs no abnormal values
- Significant increased risk of:
  - Macrosomia
  - Neonatal hypoglycemia
  - C-section
  - Gestational hypertension
  - NICU admission
  - Neonatal respiratory distress

AJOG American Journal of Obstetrics & Gynecology

Ann Intern Med. 2013 Jul 16;159(2):123-9. doi: 10.7326/0003-4819-159-2-201307160-00661.

Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research.

Hartling L[1], Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L.

- Metaanalysis of RCTs and cohort studies
- Compared diet modification, glucose monitoring, and insulin with no treatment
- Treatment group with fewer cases of:
  - Preeclampsia
  - Macrosomia
  - Shoulder dystocia
- Treatment group had more office visits

U.S. Preventive Services TASK FORCE

Glycemic control targets

- ADA and ACOG:
  - Fasting <95
  - 1 hour postprandial <140
- MUSC targets:
  - Fasting <90
  - 1 hour postprandial <130
  - A1C under 6%

Treatment Goals

- Achieve euglycemia
- Decrease risk of adverse perinatal outcome

- Insulin only FDA approved treatment

TREATMENT OF GDM

Insulin
Metformin
Glyburide

Long Acting Insulin

Long acting Insulins in Pregnancy

- Avoid peak action
- Less symptomatic hypoglycemia
- Less nocturnal hypoglycemia
- Result in tighter control

Comparison of All agents

Comparative Efficacy and Safety of OADs in Management of GDM: Network Meta-analysis of Randomized Controlled Trials

Yun-Fa Jiang,* Xue-Yan Chen,* Tao Ding, Xiao-Feng Wang, Zhong-Ning Zhu, and Su-Wen Su

- 18 RCT's comparing efficacy and safety between different OADs or OAD vs Insulin in GDM
- 30-733 pts (10 had < 100 pts and 13 <150 pts)

J Clin Endocrinol Metab, May 2015, 100(5):2071–2080

Comparison of All agents

- No significant difference in
  - Fasting blood glucose
  - Hb A1C
- Metformin
  - Lower maternal weight gain
- Glyburide
  - Higher neonatal birth weight
  - Increased incidence of neonatal hypoglycemia
  - Increased incidence macrosomia

J Clin Endocrinol Metab, May 2015, 100(5):2071–2080

ACOG Practice Bulletin #180, July 2017

- Recommendation for insulin as first line therapy
- Treatment with glyburide compared with insulin demonstrated worse neonatal outcomes:
  - Respiratory distress syndrome
  - Hypoglycemia
  - Macrosomia
  - Birth injury
- Treatment with metformin compared with insulin:
  - Lower rate of gestational hypertension
  - Less maternal weight gain
- 20-40% of women will fail therapy with metformin or glyburide alone:
  - Both cross placenta
  - Lack of long term follow up of exposed neonates
- Metformin is second line therapy if the patient is unable to comply with insulin

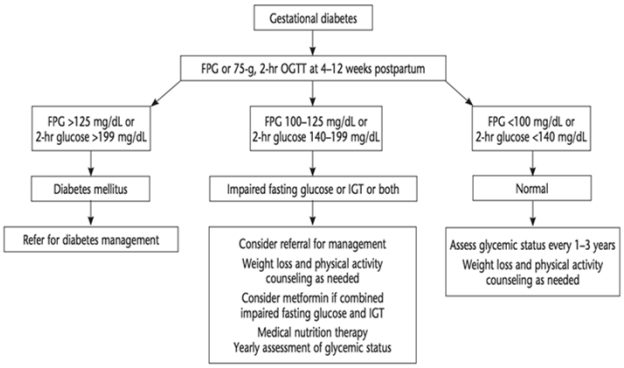
First line GDMA2 treatment: Insulin

- NPH (Novalin, Humalin): **Cloudy**
  - Intermediate acting insulin
  - To control fasting glucose, begin bedtime NPH at 0.2 unit/kg
  - Onset of action 1-3 hours
  - Peak 5-7 hours
  - Duration 13-18 hours
- Novolog(aspart)/Humalog (lispro): **Clear**
  - Short acting insulin for meal coverage
  - Can be targeted for abnormal values at single time of day
  - Onset of action 1-15 minutes
  - Peak 1-2 hours
  - Duration 4-5 hours

GDMA2

- Antenatal testing beginning at 32 weeks
- EFW every 4 weeks
- Recommend A1C q4-6 weeks to confirm compliance
- Serial assessment of amniotic fluid
- Well controlled: delivery between 39 0/7-39 6/7
- Consideration of primary c-section if EFW > 4500g

Postpartum 2 hour GTT



ACOG
THE AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS

Take home points:

- Preconception counseling- Goal A1C <6%
- DM 1 – must take basal insulin
- Screen all women at risk diabetes at the initial Ob visit or in the first trimester
- The risk of recurrent GDM in a subsequent pregnancy is 40%
- Insulin is the first line treatment to achieve glucose targets
  - To control fasting glucose, begin bedtime NPH at 0.2 unit/kg
  - If insulin is not an option, the first line oral treatment is metformin
  - Extended release metformin such as 1000mg ER qday is preferred to decrease GI side effects
- Patients with GDM need postpartum screening for DMII

Learning Assessment Question #1

Which of the following does **NOT** describe a physiologic change that occurs during pregnancy which can have a negative impact on diabetes?

a) Fetal and placental use of maternal glucose
b) Impaired action of maternal insulin
c) Compensated maternal respiratory acidosis
d) Dehydration caused by emesis

Learning Assessment Question #2

- True/False: A pregnant woman passes the first trimester early glucose tolerance test. She is no longer required to undergo a glucose tolerance test at 24-28 weeks gestation.

FALSE

Learning Assessment Question #3

- True/False: The risk of fetal anomalies increases with increasing maternal HbA1C.

TRUE

Learning Assessment Question #4

The first-line treatment option for gestational diabetes is:

a) Glyburide
b) Metformin
c) Insulin
d) Exenatide

References

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