

Diabetes in Women of Childbearing Age



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2018 Clinical Practice Guidelines

Diabetes and Pregnancy

Chapter 36

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conflict of interests

- merck
- sanofi
- novonordisk
- eli lilly
- bms
- astrazeneca
- jansenn

disclosures

- **No disclosures for this presentation**

PERSONAL USE ONLY

ROLE OF FAMILY MD IN DIABETIC WOMEN OF CHILDBEARING YEARS

- A) MINIMAL ROLE
- B) IMPORTANT ROLE
- C) NO ROLE

PERSONAL USE ONLY

COUNSELING FOR DIABETIC WOMEN OF CHILDBEARING YEARS

- **A) I DON'T DISCUSS
THIS TOPIC**
- **B) I BRING IT UP EACH
VISIT**
- **C) I ONLY DISCUSS IF
PATIENTS ASK**

OPTIMAL A1C FOR WOMEN TRYING TO GET PREGNANT

- 1) 0.06 AND LESS
- 2) 0.065 AND LESS
- 3) 0.07 BUT AIM FOR 0.065 IF CAN BE DONE SAFELY
- 4) .075

PERSONAL USE ONLY

WHAT MEDS ARE SAFE TO GET PREGNANT WITH

- A) METFORMIN
- B) DIABETA
- C) METFORMIN AND DIABETA
- D) DPP4
- E) SGLT2 INHIBITOR
- F) GLP1 AGONIST

WHAT DO YOU TELL WOMEN ON ACE; ARB AND STATIN WHO WANT TO GET PREGNANT

- A) CONTINUE UNTIL PREGNANT
- B) STOP BEFORE PREGNANCY
- C) NOT SURE

PERSONAL USE ONLY

Diabetes in Pregnancy: 2 Categories

Pregestational diabetes	Gestational diabetes
<p data-bbox="241 554 788 668">Pregnancy in pre-existing diabetes</p> <ul data-bbox="285 735 743 849" style="list-style-type: none"><li data-bbox="285 735 743 792">• Type 1 diabetes<li data-bbox="285 792 743 849">• Type 2 diabetes	<p data-bbox="1116 616 1702 731">Diabetes diagnosed in pregnancy</p>

Diabetes in Pregnancy: Consider Phases

Pregestational diabetes	Gestational diabetes
1. Preconception counseling	1. Prevention, Screening & Diagnosis
2. Management during pregnancy	2. Management during Pregnancy
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Case

- 30 year old patient
- Wants to get pregnant
- Type 2 diabetes for 10 years
- on Komboglyze 2.5;1000 bid
- Complications; mild retinopathy
- Microalbumin positive

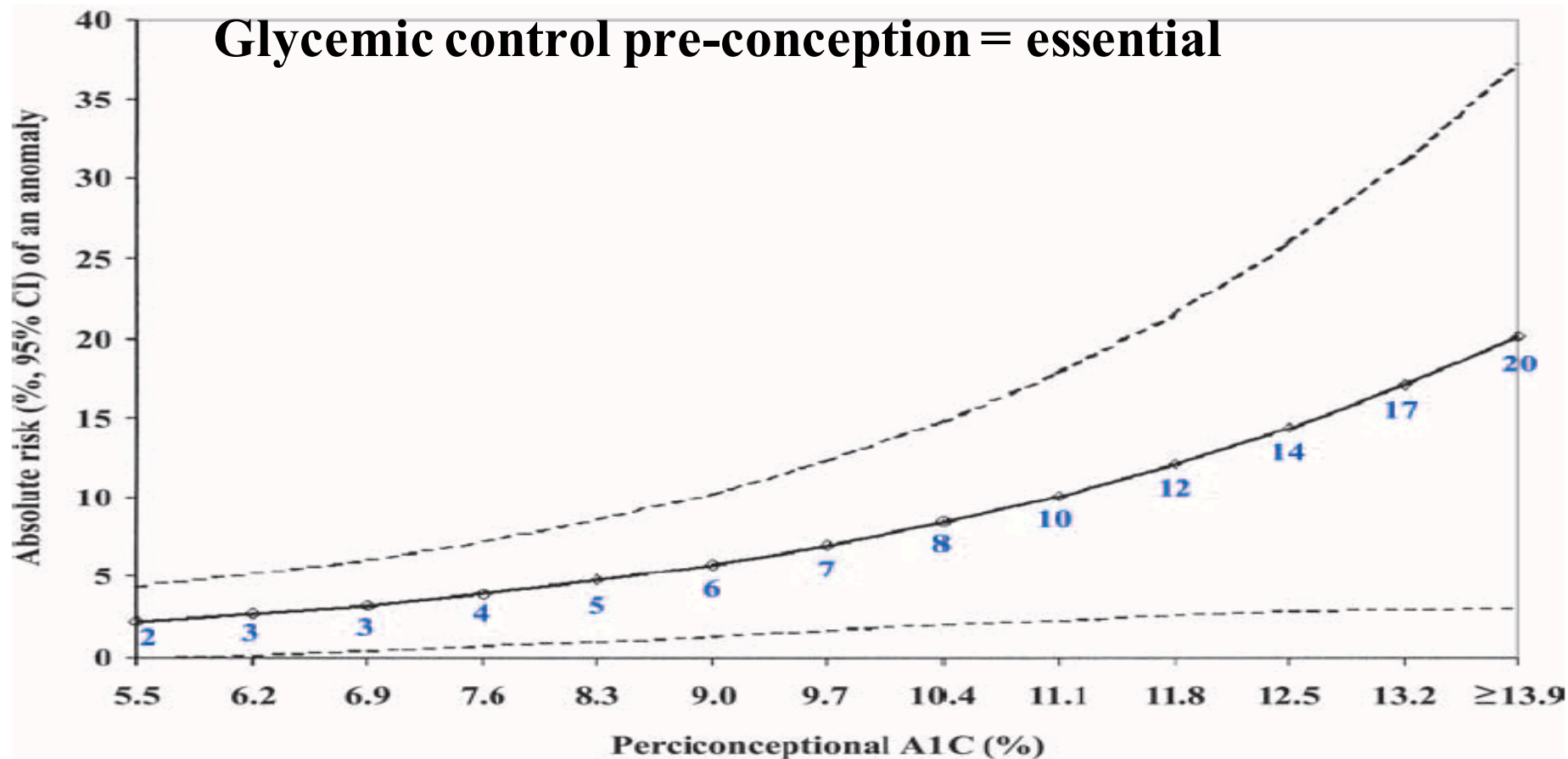
A1C 8.0%



What do you advise as her family physician?

Risk of Fetal Anomaly Relative to Periconceptional A1C

Glycemic control pre-conception = essential



Recommendation 1

Pre-existing Diabetes

Preconception care

1. All women of reproductive age with type 1 or type 2 diabetes should receive ongoing counselling on **reliable birth control**, the **importance of glycemic control prior to pregnancy**, the **impact of BMI** on pregnancy outcomes, the need for **folic acid** and the need to **stop potentially embryopathic drugs** prior to pregnancy [Grade D, Level 4]

Recommendation 2

Pre-existing Diabetes

Preconception care

2. Women with type 2 diabetes with **irregular menses/PCOS** who **lose significant weight** or are started on **metformin** or a **TZD** should be advised that **fertility may improve** and be counselled regarding possible pregnancy and receive preconception counseling [Grade D, Consensus]

Screen for Complications: Pre-pregnancy and Intrapartum

Screening for:

1.Retinopathy: Need ophthalmological evaluation

2.Nephropathy: Assess creatinine + urine albumin to creatinine ratio (ACR)

- Women with albuminuria or overt nephropathy are at ↑ risk for hypertension and preeclampsia



Preconception Checklist for Women with Pre-existing Diabetes

- ✓ Use **reliable birth control** until adequate glycemic control
- ✓ Attain a **preconception A1C of $\leq 7.0\%$** ($\leq 6.5\%$ if safe)
- ✓ May remain on **metformin + glyburide** until pregnancy, otherwise **switch to insulin**
- ✓ Assess for and manage any **diabetes complications**
- ✓ **Folic Acid 1 mg/d**: 3 months pre-conception to 12 weeks post-conception
- ✓ **Discontinue** potential embryopathic meds:
 - ✓ **ACE inhibitors / ARB** (prior to or upon detection of pregnancy in those with significant proteinuria)
 - ✓ **Statin** therapy

She is Now Pregnant!!

- She sees her endocrinologist
- Transferred to basal bolus insulin regimen
- Lantus 30 units SC qhs
- Novorapid 12 units SC ac meals
- Metformin 500 TID

- Is metformin safe?
- What do you recommend for fetal surveillance?

Recommendation 4

Pre-existing Diabetes

Preconception care

4. Women on **metformin** and/or **glyburide** preconception **may continue** on these agents if glycemic control is adequate until pregnancy is achieved [Grade C, Level 3]. Women on other antihyperglycemic agents, should **switch to insulin prior to conception** as there are no safety data for the use of other antihyperglycemic agents in pregnancy [Grade D, Consensus]

Recommendation 13

Pre-existing Diabetes

Management in pregnancy

13. Women with pre-existing diabetes should **start ASA 81 mg daily at 12-16 weeks gestation** to reduce the risk of preeclampsia [Grade D, Level 4]

Pregnancy Management for Pre-existing Diabetes

Retinopathy Surveillance

- one visit in first trimester
- visits thereafter: as needed
- more often in:
 - more severe retinopathy
 - large drop in A1C
 - poor glycemic control

Nephropathy

- Good BP control
- Watch for hypertension, preeclampsia

Pregnancy Management for Pre-existing Diabetes

- Type 1 diabetes: **Continuous glucose monitoring** should be considered in all women
 - ↓ LGA, NICU >24 hrs, neonatal hypoglycemia, infant length of hospital stay
- Encourage weight gain according to Institute of Medicine recommendations
- **ASA** to reduce the risk of pre-eclampsia, **starting at 12-16 weeks** gestational age

LGA, large for gestational age; *NICU*, neonatal intensive care unit; *ASA*, acetylsalicylic acid

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Pregnancy Management for Pre-existing Diabetes

- Perform SMBG pre- and postprandially

Target BG values	
Fasting and pre-prandial BG	<5.3 mmol/L
1h postprandial BG	<7.8 mmol/L
2h postprandial BG	<6.7 mmol/L

- Aim for **A1C $\leq 6.5\%$** ($\leq 6.1\%$ if possible)
 - Lower late stillbirth & infant death
- Individualize targets in those with severe hypoglycemia/unawareness

Pregnancy Management for Pre-existing Diabetes: Fetal Surveillance & Delivery

- Fetal surveillance should be started at 30-32 wks gestational age, then weekly from 34-36 wks until delivery
- Earlier onset and/or more frequent: those at highest risk
- Uncomplicated: induce 38-39 wks gestational age to decrease stillbirth
- Induction prior to 38 wks for other fetal/maternal indications

Recommendation 16

Pre-existing Diabetes

Fetal surveillance and timing of delivery

16. In women with pre-existing diabetes, assessment of fetal well-being should be performed at **30-32 weeks** gestation and performed **weekly starting at 34-36 weeks gestation** and continued until delivery [Grade D, Consensus]. Earlier onset and/or more frequent fetal health surveillance is recommended in those considered at highest risk [Grade D, Consensus]

MiTy Trial

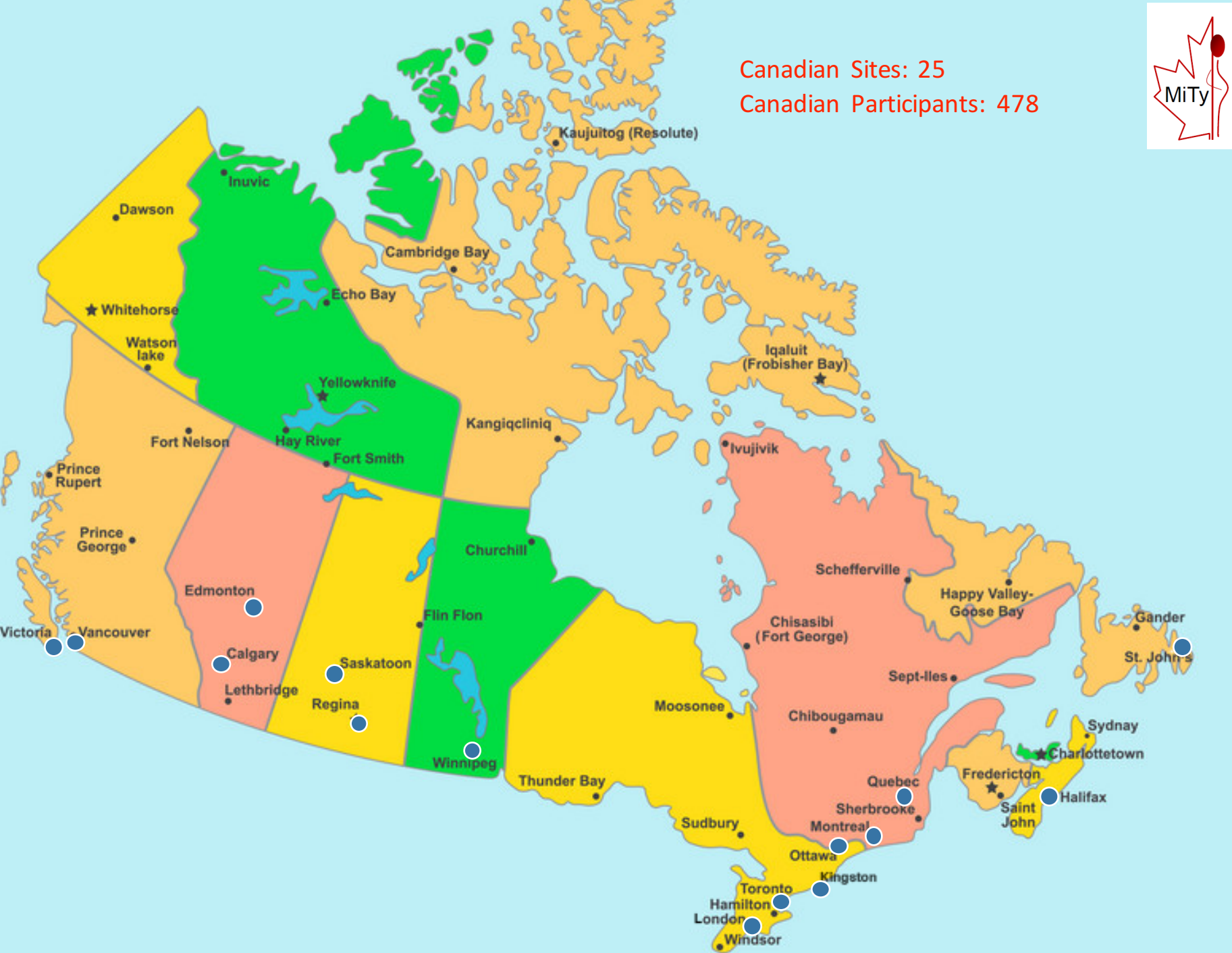


Metformin in Women with Type 2 Diabetes in Pregnancy Trial

CIHR funded study June 2010



Canadian Sites: 25
Canadian Participants: 478



Aim of the Study

Secondary Research Questions:

Maternal outcomes:

- maternal weight gain,
- maternal insulin doses
- maternal glycemic control as measured by HbA1c and capillary glucose measures, rates of maternal hypoglycemia
- pre-eclampsia and/or gestational hypertension
- rate of cesarean delivery
- number of hospitalizations prior to admission for delivery
- the duration of hospital stay for the mother

Maternal Outcomes

	Metformin	Placebo
	N=240	N=242
Maternal weight gain (kg)*		
Overall weight gain	7.2±5.3	9.0±4.7
Weekly weight gain	0.4±0.3	0.5±0.3
Last HbA1c in pregnancy‡		
% (mean±SD)	5.90%±0.78	6.10%±0.94
mmol/mol (mean±SD)	41.0±8.5	43.2±10
Mean glucose mmol/l	6.05 [0.93]	6.27 [0.9
(mmol/l)	100.0 [16.7]	112.0 [16.2]

*Overall and weekly weight gain was calculated from measured weight at randomisation.

‡ After adjusting for baseline HbA1c at randomisation



Maternal Outcomes

	Metformin	Placebo
	N=240	N=242
Total insulin dose (units/kg/day) at 34 or 36 weeks (mean±SD) [§]	1.1±1.0	1.5±1.1
Total insulin dose (units/day) at 34 or 36 weeks (mean±SD) [¶]	109.8±105.1	155.3±134.1
Long-acting (units/day) at 34 or 36 weeks (mean±SD)	42.8±46.0	55.7±47.6
Short-acting (units/day) at 34 or 36 weeks (mean±SD) ^{**}	66.9±75.1	99.1±108.1

Neonatal Outcomes



Neonatal Outcomes

	Metformin	Placebo	P-Value	Effect size
Live births	N=232	N=229		
Large for gestational age >90 th centile (adjudicated using Kramer)	50 (21.6%)	66 (28.8%)	0.07	RR 0.74 (0.54, 1.0)
Extreme large for gestational age > 97 th centile (using Kramer)	20 (8.6%)	31 (14.8%)	0.041	RR 0.58 (0.34, 0.9)
Birthweight ≥4000g	28 (12.1%)	44 (19.2%)	0.046	RR 0.65 (0.43, 0.9)
Small for gestational age < 10 th centile (using Kramer ²⁵)	30 (12.9%)	15/228 (6.6%)	0.03	RR 1.96 (1.10, 3.0)

Neonatal Outcomes

	Metformin	Placebo	P-Value	Effect size
Live births	N=232	N=229		
Preterm birth <37 weeks	60 (25.9%)	47 (20.5%)	0.16	RR 1.27 (0.91, 1.77)
Birth injury	1/231 (0.4%)	3/228 (1.3%)	0.37	RR 0.36 (0.04, 3.36)
Respiratory distress	11/231 (4.8%)	8/228 (3.5%)	0.49	RR 1.36 (0.56, 3.29)
Neonatal hypoglycemia	27/231 (11.7%)	34/228 (14.9%)	0.41	RR 0.82 (0.52, 1.30)
High level neonatal care >24 h [†]	51/231 (22.1%)	46/228 (20.2%)	0.56	RR 1.10 (0.79, 1.53)

In Summary

We found several maternal and neonatal benefits in women using metformin:

- **Reduced maternal weight gain**
- **Reduced insulin dose**
- **Improved glycemic control**
- **Reduced birthweight (218g), Extreme LGA, >4,000g**
- **Lower adiposity measures: Reduced skinfolds, abdominal circumference, fat mass**

Unanswered Questions

- **What are the predictors of SGA in our women?**
- **Are these SGA babies healthy or unhealthy?**
- **What is the impact of metformin in offspring of women with T2DM in the long-term?**
- **Will there be a benefit due to**

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Pregnancy Management for Pre-existing Diabetes:

Intrapartum Glucose Management

- Monitor closely. Keep blood glucose 4.0-7.0 mmol/L to reduce neonatal hypoglycemia
- CSII can be continued in women who choose to stay on their pump, and they or their partner can independently manage the pump



Postpartum care for pre-existing diabetes

1. Adjust insulin → at risk of hypoglycemia
2. Encourage women to breastfeed:
 - Reduce neonatal hypoglycemia, offspring obesity
3. Metformin and glyburide may be used during breastfeeding → no long term data but appears safe
4. Screen for postpartum thyroiditis in type 1 diabetes → check TSH at 2-4 months postpartum

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CASE OF GDM

- **24 year old girl**
- **born in india**
- **both parents; type 2 diabetes**
- **26 weeks pregnant**
- **glucose screen 50 gram**
- **14.2**
- **a1c 0.062**
- **started on insulin during pregnancy**
- **could she use meds**

Early Screening for Women at High Risk for Type 2 Diabetes

Women at high risk of type 2 diabetes



Screen with **A1C** (or **FPG** if A1C unreliable) in **first trimester**



A1C $\geq 6.5\%$ or FPG ≥ 7.0 mmol/L → treat like type 2 diabetes



Confirm diagnosis post-partum

Why Diagnose and Treat GDM?

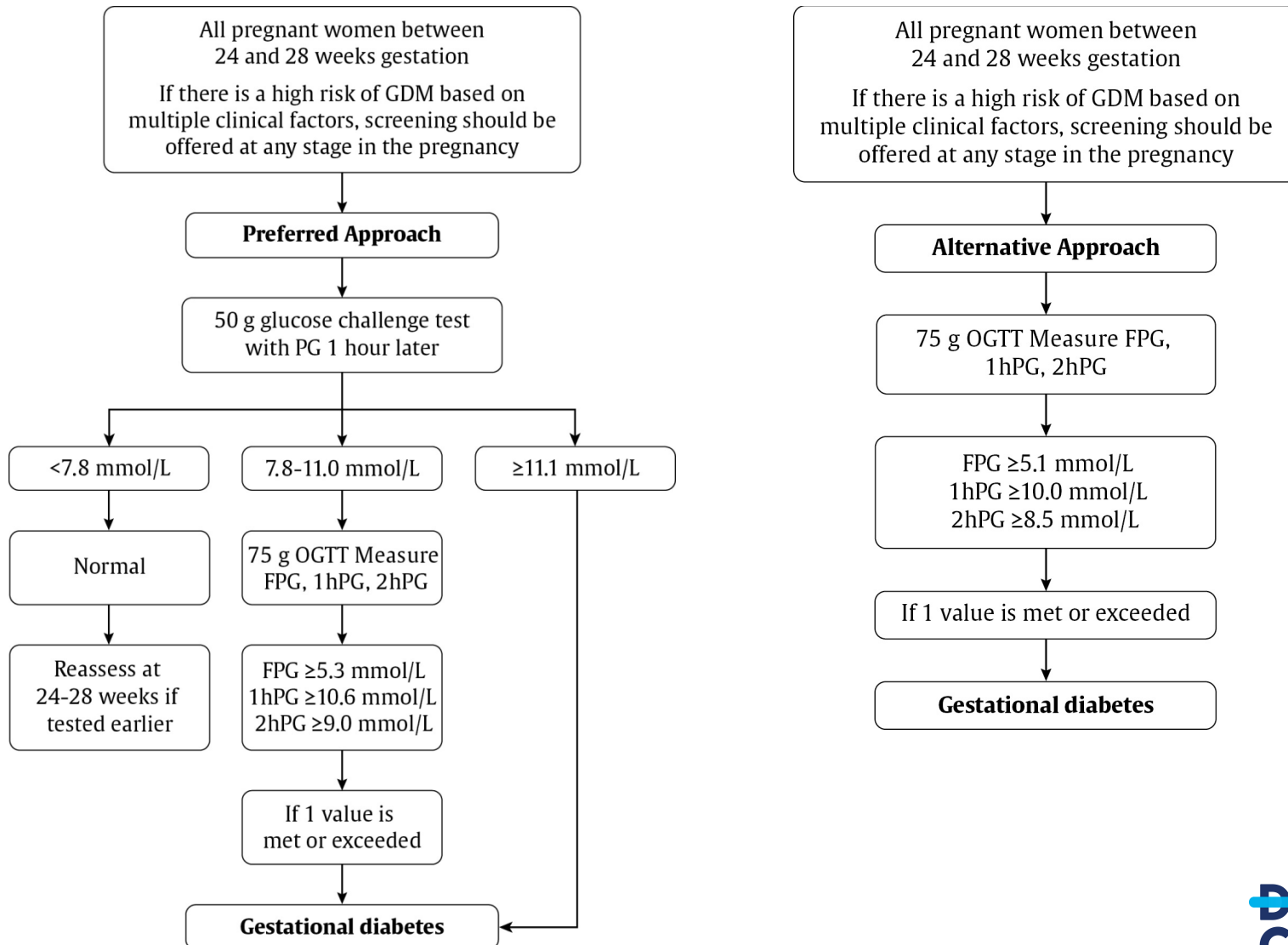
- Macrosomia
- Shoulder dystocia and nerve injury
- Neonatal hypoglycemia
- Preterm delivery
- Hyperbilirubinemia
- Caesarian section
- Offspring obesity
- Offspring diabetes

Gestational Diabetes (GDM) Screening

Universal screening for GDM
@ 24-28 weeks gestational age

Screen earlier if risk factors for GDM
(see next slide)

2018 GDM Diagnosis: Two Approaches



Recommendation 28

Gestational Diabetes

Diagnosis

28. An **alternative approach** to screen and diagnose GDM is the **1-step approach**: a **75 g OGTT** should be performed (with no prior screening 50 g GCT) as the diagnostic test for GDM using the 1 of the following criteria :

- Fasting PG **>5.1** mmol/L OR
- 1 hour PG **>10.0** mmol/L OR
- 2 hours PG **>8.5** mmol/L [Grade B, Level 1]

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GDM: Management During Pregnancy

- Receive nutrition counseling by registered dietician to achieve their nutrition, weight and blood glucose goals
- Eat healthy diet and Replace high-Glycemic Index foods with low-Glycemic Index foods to reduce need for insulin initiation and decrease birthweight
- Discuss appropriate weight gain and healthy lifestyle interventions throughout pregnancy
- Recommend weight gain according to IOM recommendations based on prepregnancy BMI interventions to reduce LGA, C-section

Institute of Medicine Guidelines for Gestational Weight Gain

Pre-Pregnancy BMI (kg/m ²)	Recommended range of total weight gain (kg)	Recommended range of total weight gain (lb)
BMI <18.5	12.5 – 18.0	28 – 40
BMI 18.5 – 24.9	11.5 – 16.0	25 – 35
BMI 25.0 – 29.9	7.0 – 11.5	15 – 23
BMI ≥30	5.0 – 9.0	11 – 20

Recommended rate of weight gain and total weight gain for singleton Pregnancies according to pre-pregnancy BMI

GDM: Management During Pregnancy

- Perform SMBG fasting and postprandially
- Glycemic targets during pregnancy:

Target BG values	
Fasting and preprandial BG	<5.3 mmol/L
1h postprandial BG	<7.8 mmol/L
2h postprandial BG	<6.7 mmol/L

- If glycemic targets not achieved within 1-2 weeks, initiate pharmacologic therapy

GDM: Management During Pregnancy

- **Insulin** first-line
 - May use aspart, lispro, glulisine: perinatal outcomes similar
- **Metformin** may be used as an alternative to insulin
 - Good safety data in pregnancy
 - Evidence of less maternal weight gain, less large-for-gestational-age, less neonatal hypoglycemia
 - Women should be informed that it crosses the placenta
 - Safety data in offspring postpartum up to 2 years
 - Insulin necessary in 40% on metformin
- **Glyburide** may be used in women who refuse insulin and not well controlled on metformin

MiG Trial - Design

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*

- **RCT 750 women with GDM**
- **Randomized to Metformin vs Insulin**
- **Primary Outcome: Composite of neonatal outcomes included hypoglycemia, respiratory distress, phototherapy, birth trauma, low 5 min APGAR, and prematurity**



DIABETA

- **studies show can be used for gdm (2000 Langhers)**
- **80 percent as effective as insulin**
- **but recently adverse neonatal outcomes such as hypoglycemia; has limited its use to third line after insulin and metformin**

Recommendation 34

Gestational Diabetes

Management during pregnancy

34. In women with GDM who **decline insulin and do not tolerate or are inadequately controlled on metformin, glyburide** may be used [Grade B, Level 2]

Recommendation 36

Gestational Diabetes

Fetal surveillance and timing of delivery in GDM

36. Women with GDM can be offered **induction** of labour between **38-40 weeks** gestation to potentially reduce the risk of stillbirth [Grade D, Consensus] and the risk of caesarean section [Grade C, Level 2]. Earlier or later induction of labour should be considered based on glycemic control and the presence or absence of other comorbid conditions [Grade D, Consensus]

GDM: Glycemic Management During Labour and Delivery

- Keep maternal blood glucose between 4.0 and 7.0 mmol/L → reduce risk of neonatal hypoglycemia

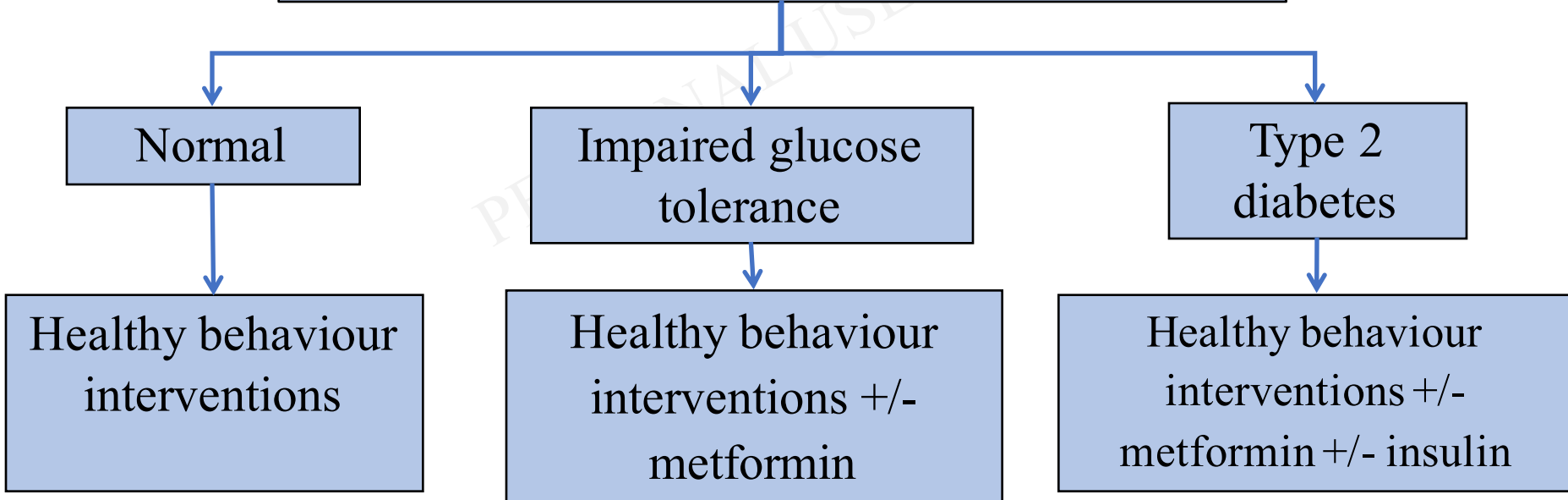
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GDM: Postpartum OGTT

75 g oral glucose tolerance test
• 6 weeks to 6 months
• If diagnosed with diabetes early in pregnancy, do FPG or OGTT at 6-8 weeks postpartum



FPG, fasting plasma glucose; OGTT, oral glucose tolerance test

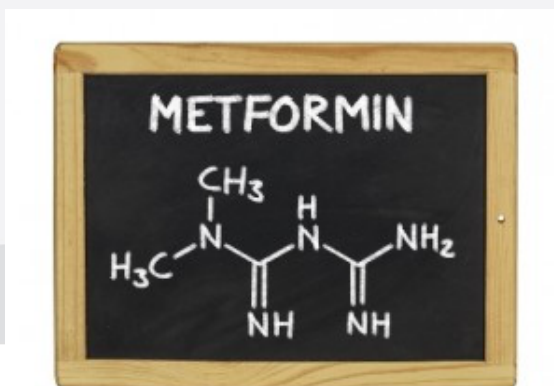
Breast feeding

- **mothers that nurse**
- **lower body weight**
- **improved insulin secretion**
- **less diabetes at 10 years**
- **longer duration and more intense should be encouraged**
- **mothers with gdm may initiate nursing but have harder time continuing**



IGT AFTER GDM

- DPP STUDIES A GDM GROUP
- LIFESTYLE AND METFORMIN CAN DECREASE TYPE 2 DM IN GDM WITH IGT
- SHOULD BE OFFERED TO PATIENTS
- RESULTS ARE IMPRESSIVE





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Diabetes Canada Clinical Practice Guidelines

www.guidelines.diabetes.ca – for health-care providers

1-800-BANTING (226-8464)

www.diabetes.ca – for people with diabetes