Second Global Conference on Health and Lifestyle

Diabetes, Obesity – The Seemingly Unending Continuum: Breaking the Chain!

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Disclosure

I have no financial or other interests which pose a conflict of interest.

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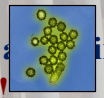
Answer this question:

"When I think of 'global pandemics,' I think of…?"

Then:

- "Black death," 1918 Spanish flu, cholera
- Tuberculosis (1880s), polio (1900s), malaria
- HIV/AIDS, SARS, 2009 H1N1 "swine" flu



Now:

When *I* think of "global pandemics," *I* [illegible]ink of…

Diabetes and Obesity!

3

Obesity: The 21st Century Global Pandemic

- Worldwide, approximately 1.6 billion adults (age 15+) are overweight (BMI > 25)
  - At least 400 million adults are obese
  - Nearly 43 million children under the age of 5 are overweight
- 2.6 million people die each year as a result of being overweight or obese

Risk Factors for Obesity:

- Overeating
- Lack of exercise
- Genetics
- Environment
- Some diseases and

"Experts have concluded that the chief causes of obesity are a sedentary lifestyle and overconsumption of high-calorie food."

Sources: World Health Organization. Fact sheet N°311, Obesity and Overweight. Updated March, 2011; Vainio H, Bianchini F. *IARC handbooks of cancer prevention. Volume 6: Weight control and physical activity*. Lyon, France: IARC Press, 2002.

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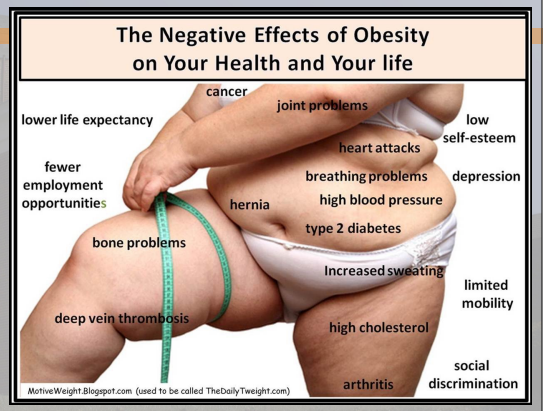
How Is Obesity Defined Clinically?

- For adults, a body mass index (BMI) of
  - ≥ 25 = Overweight
  - ≥ 30 = Obese
  - ≥ 40 = Morbid obesity
- BMI = [Wt. (lbs.) / (Ht. in in. x Ht. in in.)] x 703
  - *E.g., a 175-lb. person, who is 60 in. tall, would have a BMI of [175/(60x60)] x 703 = 34.2 (obese)*



Sources: Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention and Health Promotion; Centers for Disease Control and Prevention. Updated April 27,2012. Available at http://www.cdc.gov/obesity/adult/defining.html; BMI Classification. Global Database on Body Mass Index. World Health Organization. Updated Dec. 19, 2013. Available at http://apps.who.int/bmi/index.jsp. *Image source*: MotivateWeight.Blogspot.com

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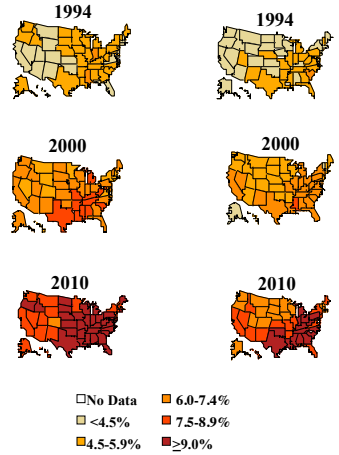
Prevalence of the "Diabesity" Epidemic

Obesity (BMI ≥30 kg/m²) **Diabetes**



Projected Increase in Diabetes by 2030

	2000	2030
The Americas	33 M	66.8 M
Africa	7 M	18.2 M
Middle East	15.2 M	42.6 M
Europe	33.3 M	42.6 M
Asia & Australasia	82.7 M	190.5 M

The top 10 countries, in numbers of people with diabetes, are:

1. India
2. China
3. USA
4. Indonesia
5. Japan
6. Pakistan
7. Russia
8. Brazil
9. Italy
10. Bangladesh

Sources: CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics; Wild S *et al. Diabetes Care*. 2004;27:1047-1053.

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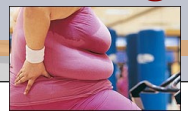
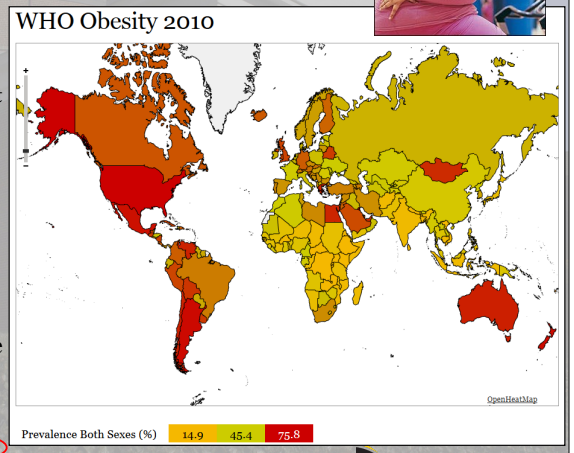
Obesity: Global Health Threat and Gaining!



- Obesity has nearly doubled since 1980s
  - 2010 global obesity prevalence:
    - U.S. ranked 5th highest (men) & 13th highest (women)
    - U.K. ranked 23rd (men) & 56th (women)
    - Canada ranked 20th (men) & 61st (women)
    - Switzerland ranked 65th (men) & 86th (women)
- Obesity is the 5th leading cause of death worldwide
- Obesity is preventable!



Sources: World Health Organization. Fact sheet N°311, Obesity and Overweight; Ono T, Guthold R, Strong K. WHO Global Comparable Estimates 2005. Updated March, 2011. *Image*: Created using OpenHeatMap.com

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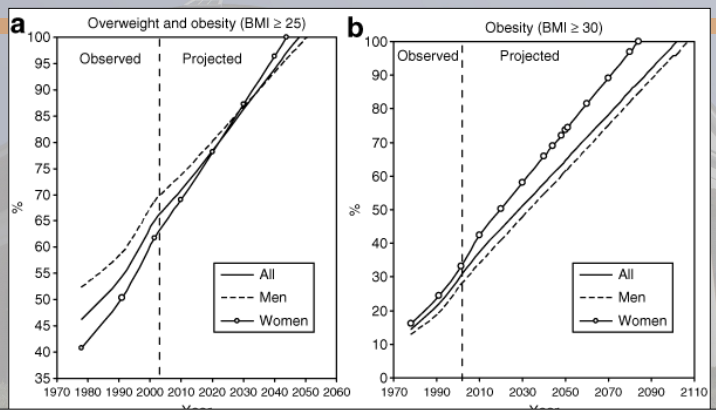
What Happens If We Do Nothing?



By 2045, 100% of Americans will be overweight;
By 2100, 100% will all be obese!

Source: Wang Y *et al. Obesity* (Silver Spring). 2008;16(10):2323-30.

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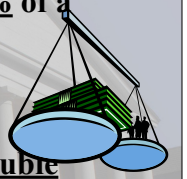
The Global Economic Burden of Obesity

- Overweight and obesity account for 0.7–2.8% of a country's total healthcare expenditures
  - In 2011, total cost in U.S. = $270B annually
  - In 2011, total cost in Canada = $30B annually
- In the U.S., obesity accounts for nearly $200 billion in additional annual medical costs, double earlier estimates.
  - Plus:
    - $9 billion annually for additional jet fuel needed to fly heavier Americans
    - $4 billion annually for additional gasoline as cars carry heavier passengers.
    - Excess chronic diseases (i.e., osteoarthritis, cardiovascular disease, and diabetes)



Sources: Withrow D, Alter DA. *Obes Rev*. 2011 Feb;12(2):131-41; Wolf AM, Colditz GA. *Obesity Research*.1998;6(2):97–106; Wolf, A. *Obesity Research*. 1998;6(suppl):2S-7S; Finkelstein, EA *et al. Health Affairs* 2009; 28(5): w822-w831.

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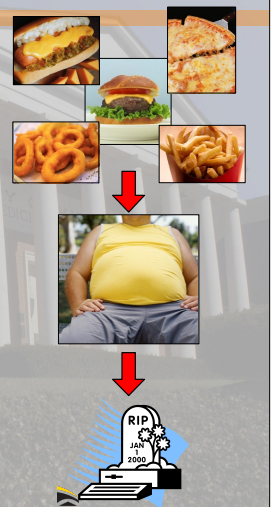
Obesity and Early Death in the United States

- An estimated 300,000 deaths per year may be attributable to obesity
- Obese adults have a 50–100% increased risk of premature death, compared to adults with a BMI of 20 to 25
- Even an extra 10–20 pounds for a person of average height increases the risk of death, especially among adults aged 30–64 yrs.



Source: Office of the Surgeon General,. Overweight and Obesity: Health Consequences. Available at: http://www.surgeongeneral.gov/topics/obesity/calltoaction/fact_consequences.htm

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Diabetes and Obesity

- Obesity is the #1 risk factor for developing type 2 diabetes mellitus (T2DM)
  - More than 1/3 of all U.S. adults are obese
  - About 12.5 million U.S. children and adolescents (aged 2 – 19 yrs.) are obese
  - As many as 80% of type 2 diabetics are obese
  - Diabetes and obesity are so closely linked that many experts refer to them as one disease state: "Diabesity"

Sources: Centers for Disease Control and Prevention. *National Diabetes Fact Sheet, 2011*; Majed SA *et al. Cardiovascular Diabetology.* 2009;8:33; Chan JM *et al. Diabetes Care.* 1994;17:961-969; Colditz GA *et al. Ann Intern Med*. 1995;122:481-486.

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Two Types of Diabetes in Pregnancy

Gestational Diabetes (GDM)

- Occurs only during pregnancy and disappears not long after delivery
- Even mild hyperglycemia may impact pregnancy outcomes
- Associated with higher incidence of:
  - Cesarean section
  - Preterm labor
  - Macrosomia
  - Shoulder dystocia or injury
  - Intensive neonatal care
  - Hyperbilirubinemia, and
  - Preeclampsia

Pregestational Diabetes (PGDM)

- Exists prior to pregnancy; can be either type 1 or type 2
- Poor diabetes control before conception/ during first trimester of pregnancy causes major consequences for both baby and mother
- Consequences for the baby include a greater risk for:
  - Major birth defects
  - Preterm birth
  - Still birth
  - Respiratory problems
  - Hypoglycemia
  - Jaundice
  - Later obesity and diabetes

Sources: Reece EA, Homko, CJ; *Contemp Ob Gyn* 2005; 50:8, 42-52; HAPO Study Cooperative Research Group et al. *N Engl J Med* 358(19):1991-2002

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Diabesity = The leading risk factor for adverse pregnancy outcomes

- Diabetic, obese women who are pregnant tend to:
  - Have longer hospital stays
  - Require more medications
  - Spend more time with their doctors than normal-weight women do
- Much of this excess morbidity is due to complications, such as high blood pressure, preeclampsia, and C-sections
- Obese, pregnant women have an increased risk of:
  - Hypertension
  - Blood clots/Thrombosis
  - Pregestational and gestational diabetes
- Fetal/postnatal complications of obesity and pregnancy incl
  - Large for gestational age
  - Birth defects
  - Late fetal death
  - Long-term sequelae (e.g., obesity, diabetes, hypertension)

Source: Chu SY *et al. N Engl J Med.* 2008;358(14):1444-53. *Photo credits:* (top & middle) UMSOM; (bottom) Wikimedia Commons/HBR

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Report of the Institute of Medicine of the National Academy of Sciences
"The Weight of the Nation"

Full series available at http://theweightofthenation.hbo.com/films

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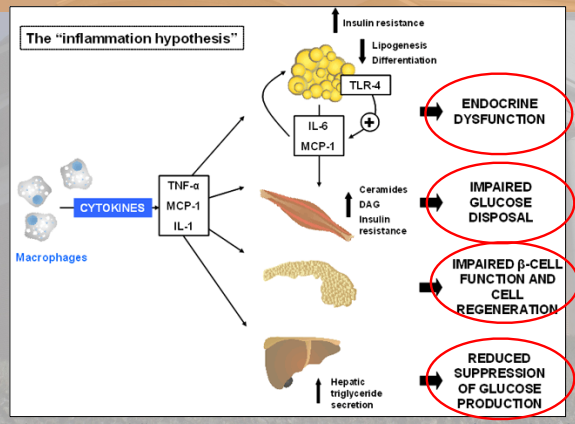
Pathophysiology of Obesity-Related Complications:
Inflammation Hypothesis



The "inflammation hypothesis" asserts that obesity represents a state of chronic inflammation where inflammatory molecules produced by infiltrating macrophages in adipose tissue exert pathological changes in insulin-sensitive tissues and β-cells.

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Diabetes and the Offspring of the Obesity Continuum:
3 Key Questions That Research Must Address

- Does maternal diabetes in pregnancy set the stage for health problems for infants?
  - Vascular complications
  - Insulin resistance
  - Type 2 diabetes

- What is the link between diabetes and birth defects?
- How can we improve diabetic pregnancy outcomes for the mother, fetus, and the mature adult?

Photo credits: Wikimedia Commons/Jaap Vermeulen; UMSOM

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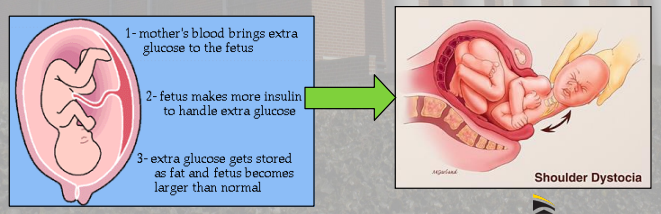
Maternal-Child Consequences of Obesity

- Obese women who become pregnant have:
  - 3- to 8-times higher risk of developing GDM vs. normal weight women
  - Amt. of weight gained during pregnancy has greater impact on GDM risk than prepregnancy BMI
- Babies born to obese women have an increased risk for:
  - Macrosomia
  - Shoulder dystocia
  - Neural tube defects



Source: Chu SY *et al. Diabetes Care*. 2007;30(8):2070-6.

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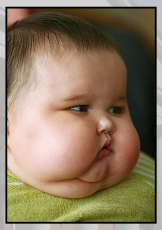
Diabetes and the Offspring of the Multi-generational Obesity Continuum

- Babies born to obese mothers are more likely to develop:
  - Obesity by age 4 yrs. old
  - Diabetes in early adulthood
  - Cardiovascular problems
- Between 16–33% of U.S. children and adolescents are obese
- Obesity most commonly begins in childhood between ages 5–6, and during adolescence
- A child who is obese between ages 10–13 has an 80% chance of becoming an obese adult



Sources: Stothard KJ *et al. JAMA*. 2009;301(6):636-50; Olson CM *et al. Child Obes*. 2010;6(4):201-207.

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Does Maternal Diabetes Cause Health Complications in Offspring Later in Life?

- Renal problems in offspring linked to maternal diabetes in pregnancy
  - Reduced nephron number can lead to
    - Glomerular hypertension & proteinuria
    - Activation of renin-angiotensin system
    - Rise in blood pressure & renal damage
- Cardiovascular problems in offspring linked to maternal diabetes in pregnancy
  - Altered/impaired angiogenesis can lead to vascular dysfunction
  - Endothelial dysfunction can lead to impaired vascular system development
- Maternal diabetes in pregnancy linked to long-term diabetes, obesity and insulin resistance in offspring

Sources: Amri K et al. Diabetes. 1999;48(11):2240-5; Boubred F et al. Am J Physiol Renal Physiol. 2007;293(6):F1944-9; Tran S et al. J Am Soc Nephrol. 2008;19(5):943-52; Chen YW et al. Am J Physiol Renal Physiol. 2001;300(1):F147-56; Brenner BM, Garcia DL, Anderson S. Am J Hypertens. 1988;1(4 Pt 1):335-47; Simeoni U, Barker DJ. Sem Fetal Neonatal Med. 2009;119-124; Larger E et al. Diabetes. 2004;53(3):752-61; Pinter E et al. Am J Pathol. 2001;158(4):1199-206; Ingram DA et al. Diabetes. 2008;57(3):724-31; Holeman K et al. Diabetologia. 1999;42(1):81-9; Madri JA, Enciso J, Pinter E. Pediatr Dev Pathol. 2003;6(4):334-41; Buckley AJ *et al. Metabolism*. 2005;54(4):500-7; Aerts L *et al. Am J Obstet Gynecol*. 1988;159(5):1287-92; Serradas *et al. Diabetes*. 2002;51(2):392-7; Dabelea D. *Diabetes Care*. 2007;30(Suppl. 2):S169-74.

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Obesity Links to Congenital Birth Defects: *Atlanta Birth Defects Risk Factor Surveillance Study*

- Population-based case-control study of mothers who had infants in 5-counties around metropolitan Atlanta
  - Maternal prepregnancy weight (pre-existing diabetes excluded):
    - Obese = BMI ≥ 30
    - Overweight = BMI 25.0–29.9
    - Average-weight = BMI 18.5–24.9
- Findings:
  - Infants born to obese women have higher risks than infants born to
    - Spina bifida (OR: 3.5, CI: 1.2-10.3)
    - Heart defects (OR: 2.0, CI: 1.2-3.4)
    - Omphalocele (OR: 3.3, CI: 1.0-10.3)
    - Multiple anomalies (OR: 2.0, CI: 1.0-3.8)
  - Infants born to obese women have higher risks than infants born to overweight women
    - Heart defects (OR: 2.0, CI: 1.2-3.1)
    - Multiple anomalies (OR: 1.9, CI: 1.1-3.4)
- Conclusions:
  - Maternal obesity & overweight linked to birth defects: spina bifida, omphalocele, heart defects and multiple anomalies

Sources: Watkins ML, et al. Maternal obesity and risk for birth defects. *Pediatrics* 2003, 111:1152-1158. *Photo credit*: NeuroWiki

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The BIG Question:

Why do women with diabetes deliver more infants with birth defects?

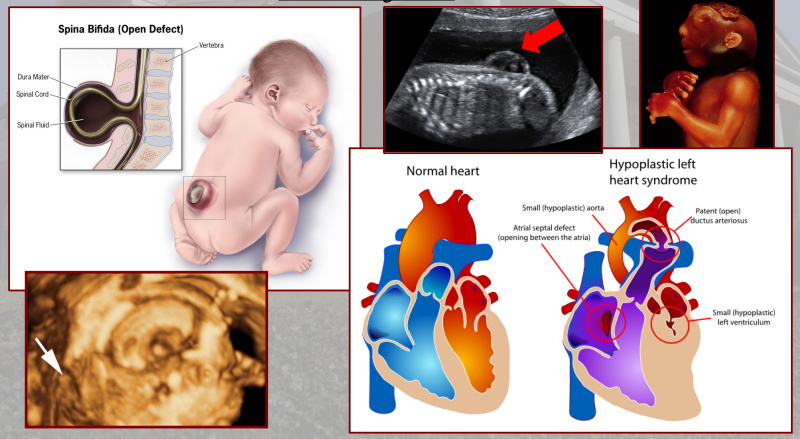

Photo credits: (clockwise from top left) Wikimedia Commons/Ed Uthman, MD ; Wikimedia Commons/Wolfgang Moroder; Wikimedia Commons/Mariana Ruiz; UMSOM; CDC; NeuroWiki

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Link Between Diabetes and Birth Defects

1st trimester HbA_1 levels (SD above mean)	% of infants with major malformations (n)	Risk Ratio (95% confidence interval)
≤ 6	3 (99)	1.0
6.1-9.0	5.2 (77)	1.7 (0.4-1.7)
9.1-12.0	4.3 (46)	1.4 (0.3-8.3)
12.1-15.0	38.9 (18)	12.8 (4.7-35.0)
>15.0	40.0 (10)	13.2 (4.3-40.4)

↑Hyperglycemia = ↑Rate of defects

- **In the United States:**
  - **4 in 10 babies with a congenital heart defect die**
  - **1 in 10 babies with a neural tube defect die**
- **Birth defects occur in 6–10% of newborns of diabetic mothers (3% background)**
- **In 2010, 8,000 babies were born with a birth defect caused by diabetes**

Sources: Greene MF. *Teratology*. 1989:39:225. Sheller *et al. Toxicological Sci.* 2008;105(1):166-172

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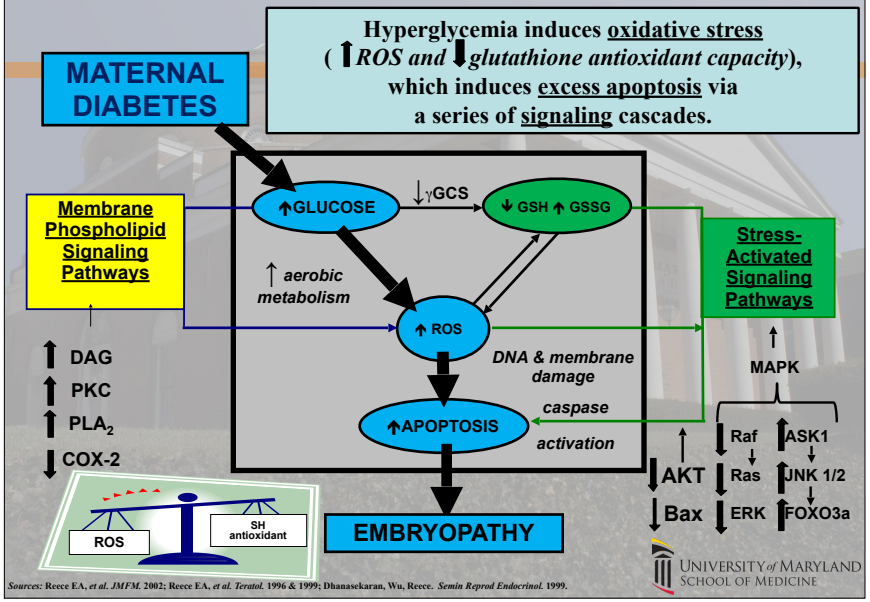
What Is The Experimental Hypothesis on Causation?

Hyperglycemia induces oxidative stress (↑*ROS and* ↓*glutathione antioxidant capacity*), which induces excess apoptosis via a series of signaling cascades.



Sources: Reece EA, *et al. JMFM.* 2002; Reece EA, *et al. Teratol.* 1996 & 1999; Dhanasekaran, Wu, Reece. *Semin Reprod Endocrinol.* 1999.

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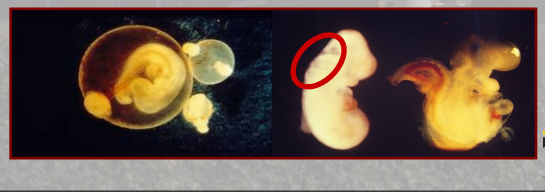
Is Hyperglycemia a Teratogen?

	Number of Embryos	Glucose Level (mg/dl)	NTD Rate (%)	Resorption Rate (%)
Non-diabetic Group (10)	162	110.8 ±18	1.25 ± 0.8	0.59 ± 0.2
Diabetic Group (10)	139	312.7 ± 30*	28.45 ± 3.9*	11.2 ± 3.1*

* Significant difference (P<0.05)



Maternal diabetes increased NTD rate by more than 20-fold

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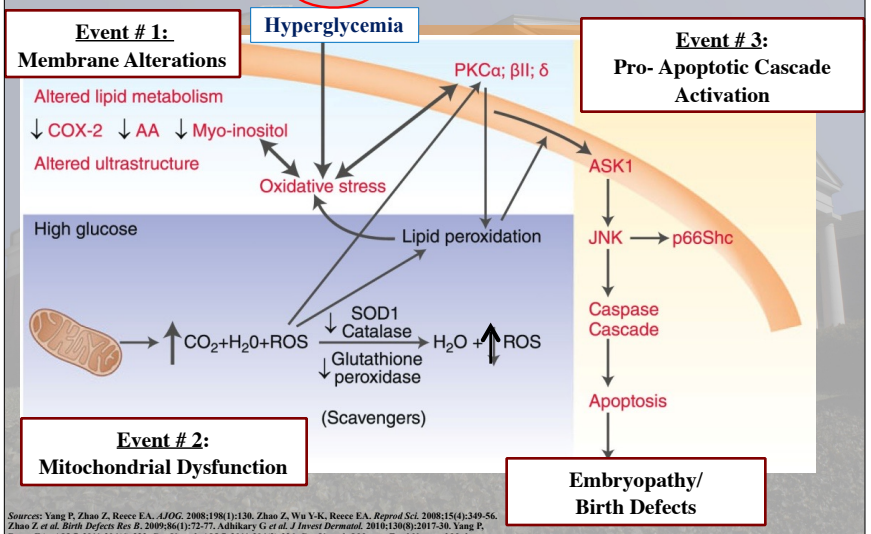
Hyperglycemia Leads to at Least Three Biomolecular "Events"



Sources: Yang P, Zhao Z, Reece EA. *AJOG.* 2008;198(1):130. Zhao Z, Wu Y-K, Reece EA. *Reprod Sci.* 2008;15(4):349-56. Zhao Z *et al. Birth Defects Res B.* 2009;86(1):72-77. Adhikary G *et al. J Invest Dermatol.* 2010;130(8):2017-30. Yang P, Reece EA. *AJOG.* 2011;204(4):332. Cao Y *et al. AJOG.* 2011;204(3):226. Cao Y *et al. J Matern Fetal Neonatal Med.* 2012;25(10):2020-4. Zhao Z, Eckert RL, Reece EA. *Reprod Sci.* 2012;19(8):823-31.

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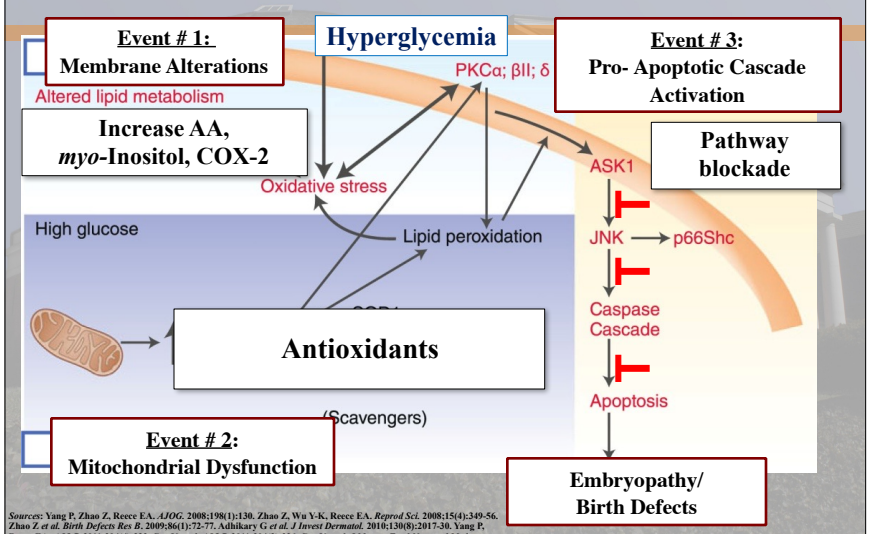
What are Potential Targets for Intervention?



Sources: Yang P, Zhao Z, Reece EA. *AJOG.* 2008;198(1):130. Zhao Z, Wu Y-K, Reece EA. *Reprod Sci.* 2008;15(4):349-56. Zhao Z *et al. Birth Defects Res B.* 2009;86(1):72-77. Adhikary G *et al. J Invest Dermatol.* 2010;130(8):2017-30. Yang P, Reece EA. *AJOG.* 2011;204(4):332. Cao Y *et al. AJOG.* 2011;204(3):226. Cao Y *et al. J Matern Fetal Neonatal Med.* 2012;25(10):2020-4. Zhao Z, Eckert RL, Reece EA. *Reprod Sci.* 2012;19(8):823-31.

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How Can We Improve Outcomes Among Diabetics in General?

- Diabetes Control and Complications Trial (DCCT) in 1983- 1993:
  - Examined whether euglycemia could slow onset of diabetic kidney disease, eye disease and nerve damage
  - 10-year study conducted at 29 institutes in the U.S. and Canada
  - Enrolled 1,441 participants (aged 13 – 39 yrs.) with T1DM
  - Participants randomly assigned to 2 groups:
    - Group 1: standard care
    - Group 2: intensive glycemic control
  - Results:
    - 50% reduced risk of kidney disease
    - 76% reduced risk of developing eye disease; 54% reduction in progression of eye disease
    - 60% reduced risk of nerve damage

Conclusion: Tight glycemic control can prevent or slow progression of diabetes complications

Source: Diabetes Control and Complications (DCCT) Research Group. *Kidney Int.* 1995;47(6):1703-20. *Photo credit*: Wikimedia Commons/Mr. Hyde.

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How Can We Improve Outcomes Among Diabetics in General?

- UK Prospective Diabetes Study Group (original study from 1977-1997, with follow-up study from 1998-2008)
- Conducted at 20 hospital clinics in England, Scotland and Northern Ireland
  - Overall study enrolled over 5,000 participants (aged 25 – 65 yrs.) with T2DM; results reported in 1998 & 2008
  - Smaller study looked at 1,148 participants with T2DM and hypertension; results reported in 1998
- Results: Tight glycemic control (insulin) reduced
  - Any diabetes complication by 12% (1998) and 9% (2008)
  - Microvascular complications by 25% (1998) and 24% (2008)
  - Risk of myocardial infarction by 16% (1998) and 15% (2008)
- Results: Tight blood pressure control (ACE inhibitor or beta-blocker) reduced
  - Risk of stroke by 44%
  - Progression of retinopathy by 34% and loss of visual acuity by 47%
  - Diabetes-associated deaths by 32%
- ***Conclusion***: Tight glycemic & blood pressure control can significantly reduce incidence of diabetes-associated deaths and vascular complications

Source: UK Prospective Diabetes Study Group. *BMJ.* 1998;317(7160):703-13; Holman RR *et al. N Engl J Med.* 2008 Oct 9;359(15):1577-89.

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How Can We Improve Outcomes of Diabetic Pregnancies?
Glycemic Control to Prevent Diabetes-Associated Birth Defects

Investigator	Control Group			Study Group		
	# Patients	Malformation Rate (%)	Glucose Control	# Patients	Malformation Rate (%)	Glucose Control
Pedersen et al. (1979)	*284*	*14.1*	*Inadequate*	*363*	*7.4*	*Improved*
Fuhrmann et al. (1983)	*128*	*7.5*	*87.1% blood Glu readings btw 2.3-7.7 mmol/L achieved by 9.79% of patients*	*292*	*0.8*	*87% blood Glu readings btw 2.3-7.7 mmol/L achieved in all patients*
Fuhrmann et al. (1984)	*144*	*6.2*	*HbA1c ≥ 10.4 ± 0.471*	*56*	*1.7*	*HbA1c ≤ 7.39 ± 0.49*
Goldman et al. (1986)	*31*	*9.6*	*HbA1c <9% in 47% of patients*	*44*	*0*	*HbA1c < 9% in 87% of patients*
Kitzmiller et al. (1986)	*53*	*15.1*		*46*	*2.2*	
Steel et al. (1988)	*65*	*9.2*		*46*	*2.2*	
Mills et al. (1988)	*279*	*9.0*	*"Late Entry"*	*347*	*4.9*	*"Early Entry"*
Damm et al. (1989)	*61*	*8.2*	*Mean HbA1c 7.3 ± 1.5*	*193*	*1*	*HbA1c 7.1 ± 1.2*
Kitzmiller et al. (1991)	*110*	*25*	*HbA1c > 10.6*	*84*	*1.69*	*HbA1c < 7.9*
Wilhoite et al. (1993)	*123*	*6.5*		*62*	*1.6*	

Source: Reece EA, Homko CJ. *Clin Obstet Gynecol.* 2000;43(1):32-41.

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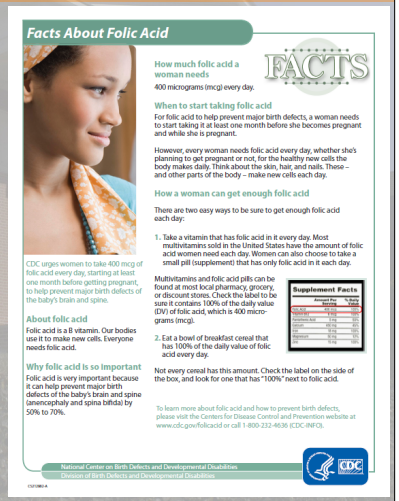
How Have We Addressed Diabetes Management?
CDC Recommendations on Folic Acid Supplements

- CDC recommends:
  - Women of childbearing age (15–45 yrs.) should consume 0.4 mg of folic acid daily to prevent NTDs
  - Women who already have had an NTD-affected pregnancy should consume 4 mg of folic acid daily, even when not planning to become pregnant
- IOM recommends:
  - Women should take 0.4 mg of synthetic folic acid daily (from fortified foods, supplements or a combination of the two), in addition to consuming dietary folate
- U.S. Preventive Services Task Force recommends:
  - Women planning or capable of pregnancy should take a daily supplement containing 0.4–0.8 mg of folic acid



Source: CDC folic acid recommendations; available at http://www.cdc.gov/ncbddd/folicacid/recommendations.html.

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How Can We Improve Outcomes of Diabetic Pregnancies?
Vitamin Supplements Prevent Diabetes-Associated Birth Defects

- Correa *et al.* 2003 study:
  - Infants born from 1968–1980 to metro Atlanta residents
  - Population-based control study (n > 6,000 infants)
  - Maternal diabetes onset before birth
  - Multivitamin use: 3 months prior to pregnancy through 1st trimester

Atlanta Study: Results				
Maternal Diabetes	Use of Vitamins	No. Cases/ Controls	OR	95% CI
Yes	Yes	1/7	0.15	0.00-1.19
Yes	No	15/11	3.93	1.79-8.63
No	Yes	120/424	0.82	0.65-1.03
No	No	1095/1165	Ref.	

***Conclusion*: Periconceptional use of multivitamins in diabetic mothers reduced risk of birth defects**

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Source: Correa A *et al. Pediatrics.* 2003;111(5 Pt 2):1146-51.

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Breaking the Chain: Key Components of Effective Obesity Management in Pregnancy

- Dietary improvements
- Limiting weight gain in pregnancy
- Increasing activity levels
- Surgical intervention (as a last resort)

Photo credits (clockwise from top): CDC/Amanda Mills; U.S. Department of Agriculture; Wikimedia Commons; UMSOM.

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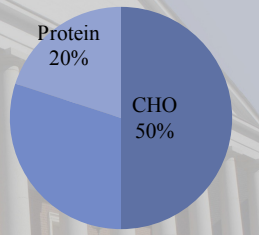
Nutritional Approach

- American Diabetic Association recommendations for pregnancy:
  - An additional 300-400 kcal/day
  - A balanced diet
    - 20% protein
    - 30% fat
    - 50% carbohydrates (CHO)
  - Bedtime snack
  - Other snacks as indicated
  - 22-30 lb. weight gain



Source: Kaiser L, Allen LH; American Dietetic Association. *J Am Diet Assoc*. 2008;108(3):553-61.

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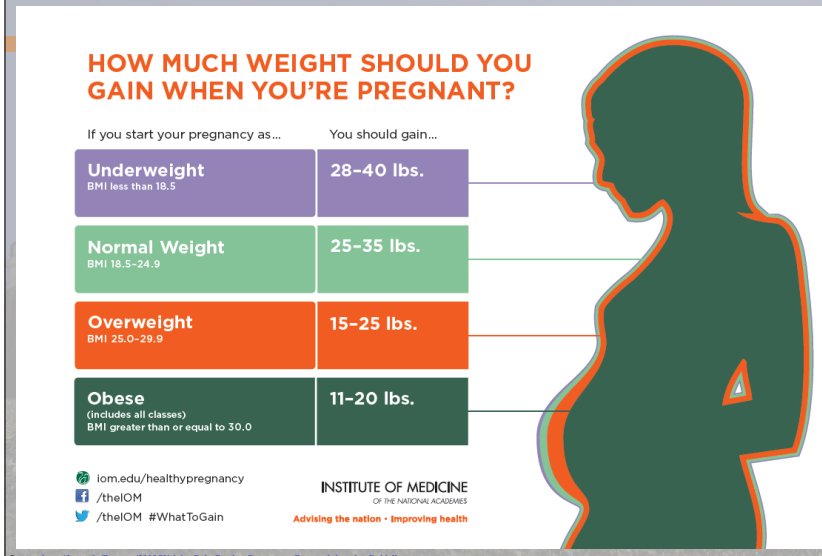
IOM Report on Healthy Weight Gain in Pregnancy



Source: http://iom.edu/Reports/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines.aspx

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Do the pregnancy weight gain standards need to change?
Evidence for more personalized weight management

- Methods: Two retrospective cohort studies (n = 410,000 women) to determine optimal weight gain during pregnancy
- Goal: Optimize birth outcomes (i.e., lower risk of preeclampsia, C-section or LGA fetus)
- Optimal weight gain:
  - Prepregnancy BMI < 20 = Weight gain of 9-22 lbs.
  - Prepregnancy BMI 20-25 = Weight gain of 5-22 lbs.
  - Prepregnancy BMI 25-30 = Weight gain of < 20 lbs.
  - Prepregnancy BMI 30-35 = Weight gain of < 13 lbs.
  - Prepregnancy BMI 35-40 = Weight gain of 0-9 lbs.
  - Prepregnancy BMI > 40 = Weight loss of 0-9 lbs.
- Conclusions:
  - For obese pregnant women, limited or no weight gain h
  - Limited weight loss improves pregnancy outcomes only

Healthy weight during pregnancy is patient-specific and should be tailored to optimize maternal and fetal outcomes

Sources: Rhodes ET *et al. Am J Clin Nutr*. 2010;92(6):1306-15; Kiel DW *et al. Obstet Gynecol*. 2007;110(4):752-8; Cedergren MI. *Obstet Gynecol*. 2007;110(4):759-64.

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How Can We Improve Outcomes of Diabetic Pregnancies?
Oral Medications for Diabetes in Pregnancy

- Review of literature:
  - Examined studies comparing insulin to glyburide or metformin published from 2007 – 2008
  - Identified randomized, controlled trials conducted in
    - U.S. (glyburide vs. insulin)
    - India (glyburide vs. insulin)
    - Brazil (glyburide vs. insulin vs. acarbose)
    - New Zealand and Australia (metformin vs. insulin)
  - Participants were diagnosed with GDM
  - Results:
    - Glyburide and metformin equivalent to insulin in terms of pregnancy outcomes in GDM
    - Rate of congenital malformations, C-sections, and abnormal birth weight babies did not differ between pregnancies treated with insulin and those treated with oral agents
- More intensive investigation of safety and feasibility of oral agents in T2DM pregnancies necessary

Sources: Nicholson *et al. Obstet Gynecol*. 2009;113(1):193-205; Paglia MJ, Coustan DR. *Curr Diab Rep*. 2009;9(4):287-90.

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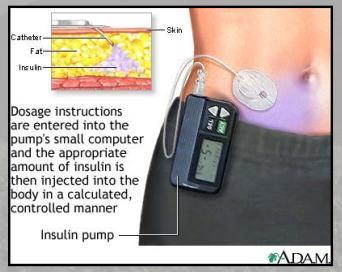
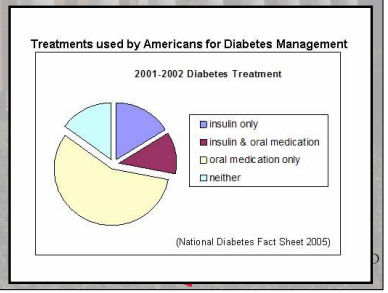
How Have We Addressed Diabetes Management?
Insulin Delivery & Non-Insulin Therapies

- Continuous insulin delivery
  - Approximately 200,000 Americans use pump therapy
  - An estimated 100,000 more are in use in other parts of the world
- Non-insulin therapies
  - For pregnant women with T1DM, insulin is treatment of choice
  - For pregnant women with T2DM, oral hypoglycemic agents may be effective





Source: Homko CJ, Reece EA. *J Matern Fetal Neonatal Med*. 2006;19(11):679-686.

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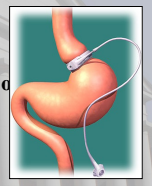
Bariatric Surgery for Obesity:
A Last Resort!

- Reduces stomach size by gastric banding or removal of a portion of the stomach
- Long-term studies show:
  - Significant long-term loss of weight (up to 8 yrs.)
    - 20-30 kg weight loss in obese patients with BMI ≥ 40 kg/m²
    - For patients with BMI of 35-40 kg/m², data supporting the superiority of surgery are inconclusive
  - Recovery from diabetes
  - Improvements in cardiovascular risk factors
  - Reduced mortality from obesity complications



- >20% of patients experience some complications (mostly minor)
  - Postoperative mortality rates of <1% have been achieved
- Almost no data on surgery to treat obesity in adolescents or children

Sources: Robinson MK. *N Engl J Med*. 2009;361(5):520-1; Managing Obesity: A Clinician's Aid. Rockville (MD):Agency for Healthcare Research and Quality;2004. 4 p. (AHRQ Pub No. 04-0082)..

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"Prescription" for Health: Prevention!
From the 16th U.S. Surgeon General

PRESCRIPTION
(Not to be used to obtain medication or to contradict your own doctor's advice)

16TH SURGEON GENERAL OF THE UNITED STATES

- Moderate physical activity, at least 5 days a week, 30 minutes per day
- Eat at least 5 servings of fruits and vegetables a day
- Avoid toxins—tobacco, illicit drugs, and *abuse* of alcohol
- Responsible sexual behavior: abstinence plus optimal protection when sexually active
- Daily participation in relaxing and stress reducing activities

Best Health Wishes
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How Have We Addressed Diabetes Prevention?
Lifestyle Intervention

- Finnish Diabetes Prevention Study (DPS) in 1993
- 3-year study conducted at 5 centers in Finland
- Examined whether dietary intervention could prevent or delay onset of T2DM
- Enrolled 522 participants (aged 40 – 64 yrs.) with prediabetes
- Participants randomly assigned to control group or lifestyle intervention group

- Results:
  - Control group
    - 20% of people developed T2DM
    - Reduced weight by 0.9 kg
  - Intervention group
    - 9% of people developed T2DM
    - Reduced weight by 3.5 kg

Conclusion: Lifestyle intervention (diet, physical exercise) can successfully prevent or delay onset of T2DM

Source: Lindström J *et al. Diabetes Care*. 2003;26(12):3230-6. *Photo credit*: CDC/Amanda Mills.

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How Have We Addressed Diabetes Prevention?
Lifestyle Intervention or Medication

- Diabetes Prevention Program (DPP) Research Study in 2002
- 3-year, large multicenter study conducted at 27 institutions across the United States
- Examined whether lifestyle intervention or treatment with oral diabetes drug could prevent or delay onset of T2DM
- Enrolled 3,234 participants (mean age = 55 yrs. old) overweight with prediabetes
- Participants randomly assigned to 3 groups:
  - Group 1: One-on-one counseling on modest weight loss through physical activity and dietary changes
  - Group 2: Metformin and standard care
  - Group 3: Placebo and standard care
- Results:
  - Group 1 risk of developing T2DM reduced by 58%
  - Group 2 risk of developing T2DM reduced by 31%

Conclusion: People at risk for developing diabetes can prevent or delay disease by losing modest weight reduction through diet & exercise or by treatment with metformin

Source: Diabetes Prevention Program Research Group. *N Engl J Med.* 2002;346:393-403. *Photo credit*: CDC/Amanda Mills.

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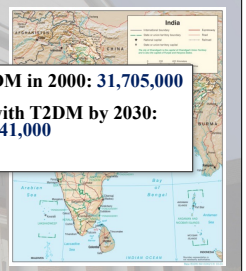
How Have We Addressed Diabetes Prevention?
Lifestyle Intervention or Medication in a High-Risk Population

- Indian Diabetes Prevention Programme (IDPP) in 2002
- 3-year study that enrolled 551 participants (aged 35 – 55 yrs.) with prediabetes
- Participants randomized to 4 groups:
  - Group 1: control
  - Group 2: lifestyle intervention
  - Group 3: metformin
  - Group 4: lifestyle intervention and metformi



# of People with T2DM in 2000: 31,705,000

Est. # of People with T2DM by 2030: 79,441,000

- Results:
  - Group 1: 55% incidence of T2DM
  - Group 2: 39.3% incidence of T2DM (reduced risk by 28.5%)
  - Group 3: 40.5% incidence of T2DM (reduced risk by 26.4%)
  - Group 4: 39.5% incidence of T2DM (reduced risk by 28.2%)

Conclusions:

- Progression to T2DM is high in Asian Indians, but lifestyle intervention and/or metformin reduces incidence of diabetes
- No added benefit of combining lifestyle intervention and metformin

Sources: Ramachandran A *et al. Diabetologia*. 2006;49(2):289-97; World Health Organization. Diabetes Programme. Country and regional data on diabetes. www.who.int/diabetes/facts/world_figures/en/index5.html. *Image source*: U.S. Central Intelligence Agency.

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Societal Strategies Against Obesity and Its Complications

- Solutions are few
  - Improve quality of diet
    - Less fats and calories
    - More fruits and vegetables
  - Increase level of activity
    - Exercise 30 min/day, 4-5 times/wk.
- People will not change willingly
  - Incentives must be provided, such as
    - Give tax breaks to the food industry for development of low-calorie, low-fat and low-cholesterol foods
    - Promote fruits, vegetables and whole grains
    - Give health insurance breaks for people who exercise and practice healthy living
    - Make fitness a part of health care
    - Make fitness a part of K-12 and college education

Photo credits: (clockwise from top) CDC/Dawn Arlotta; CDC/Amanda Mills; NIH/NIAID; USDA

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Final Thoughts From *"The Weight of the Nation"*

Featured: Emma Eggleston, MD, MPH, Director, Brigham and Women's Hospital Division of Endocrinology Pregnancy Program, Assistant Professor, Harvard Medical School

Source: http://iom.edu/Reports/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines.aspx

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Summary

- The rate of obesity has risen dramatically in the general population in recent years; as has the incidence of diabetes; Obesity is the number one risk factor for diabetes
- Obesity and diabetes (diabesity) have synergistic adverse effects and can lead to significant complications for pregnant women and their babies
- A low-glycemic diet, combined with moderate exercise, can ameliorate many of the negative consequences of obesity on pregnant women and their babies
- Weight management during pregnancy can improve birth outcomes
- Weight loss during pregnancy is not recommended, except for morbidly obese women (BMI > 40)
- Gastric bypass surgery prior to pregnancy can decrease the complications caused by obesity during pregnancy
- Preconception glycemic control can prevent diabetes-associated birth defects
- Preconceptional supplementation with antioxidants (e.g., folic acid) decrease risk of birth defects (i.e., NTDs & CCVDs)
- Women planning to become pregnant should take a multivitamin containing folic acid daily
- Lifestyle interventions include physical exercise, balanced diet and weight loss, in combination with medication (in some cases), improve maternal and fetal health outcomes

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