

The Diagnosis and Treatment of PCOS: With an Eye Toward Pregnancy

Too much insulin resulting from obesity is the villain in the cascade of events that lead to PCOS and other diabetic complications.

BY LOIS JOVANOVIC, MD

Excess fat in the visceral cavity is not just a cosmetic problem.¹ Fat concentrated in the center of the body is associated with insulin resistance.

One of the villains in the explosion of obesity in America is the food pyramid. In 1991, the American Heart Association led the charge, convincing the

In 1991, when Americans were told to decrease fat, carbohydrates and total caloric intake increased.

American Dietetic Association and then the American Diabetes Association (ADA) that fat should be minimized in Americans' diets. When Americans were told to decrease fat, carbohydrates and total caloric intake increased. Figure 1 shows the dramatic increase in the prevalence of obesity between 1991 and 2000.

HYPERINSULINEMIA IS THE VILLAIN

Obesity is associated with hyperinsulinemia; too much insulin is the true villain in polycystic ovary syndrome (PCOS). Women only have to be slightly overweight to increase their risk of type 2 diabetes. In the Nurse's Health Study,² the increase in risk began at a body mass index (BMI) >25 kg/m². As BMI increases,

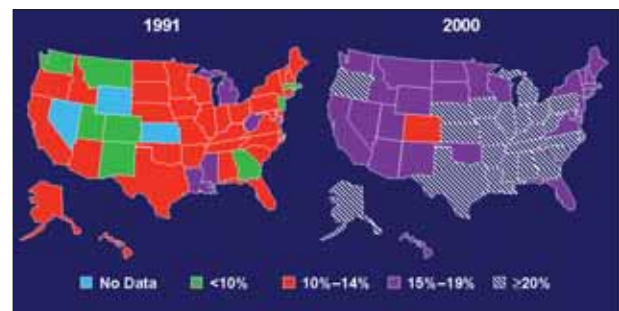


Figure 1. The increase in the prevalence of obesity from 1991 to 2000 was dramatic.

the risk for type 2 diabetes increases.

In a population of women in childbearing years in California, which has a large Mexican-American population, the prevalence of diabetes is 4%.³ Our problem is that half of these women who have type 2 diabetes do not know it. With no care, a woman with undiagnosed type 2 diabetes has a higher-risk pregnancy than that of a woman with type 1 diabetes (Figure 2).⁴ It is incumbent upon us to take care of all women of childbearing age who have a chance of developing hyperglycemia or type 2 diabetes and provide counseling prior to conception.

LARGEST MEDICAL COMPLICATION OF PREGNANCY

Diabetes or hyperglycemia has emerged as the largest medical complication of pregnancy today,

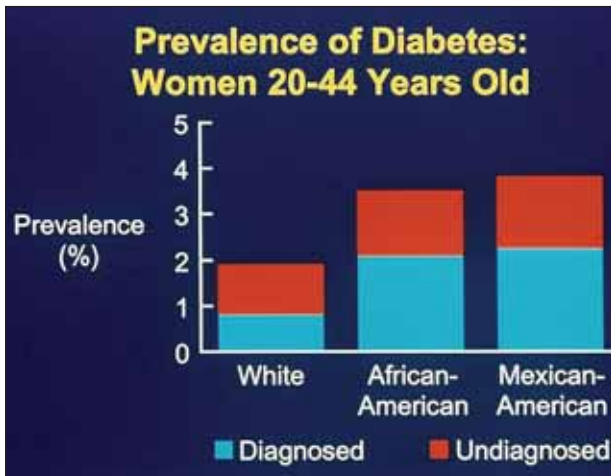


Figure 2. A woman with undiagnosed type 2 diabetes has a higher-risk pregnancy than a woman with type 1 diabetes.

affecting 8% of all pregnancies in the United States.⁵ Maternal glucose freely crosses the placenta (Figure 3), however, maternal insulin does not unless it is an immunologic insulin. If a baby receives too much nutrition in the form of glucose in utero and is also receiving maternal insulin, and if he or she has inherited the type 2 diabetes gene, the baby will tend to localize additional calories as excess fat in his or her own visceral cavity. The pairing of the type 2 gene inheritance plus overnutrition coming from the mother, sets up the insulin resistance syndrome or visceral adiposity in utero.

If this theory is correct, by normalizing maternal glucose and making sure that the insulins we use do not cross the placenta, the insulin resistance syndrome in utero, independent of the genetic predisposition to

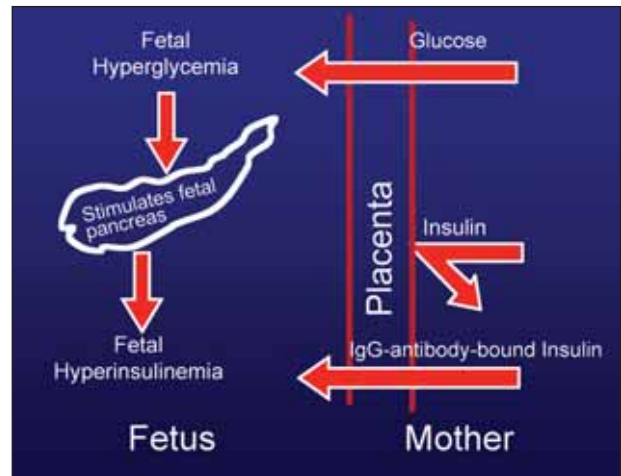


Figure 3. Maternal glucose freely crosses the placenta, but maternal insulin does not unless it is an immunologic insulin.

type 2 diabetes, would be stopped.

Peak postprandial response is the most important blood sugar value — not the average, lowest or preprandial. The highest glucose level of the day corresponds with the risk of obesity in utero or macrosomia. In 1991, our team published the first report showing the adverse effects of postprandial blood sugar.⁶ There have been subsequent reports showing that postprandial blood sugar in pregnancy is associated with macrosomia.

VISCERAL ADIPOSITY EXISTS IN UTERO

In an MRI study we conducted in collaboration with radiologists, we were able to see that heavy babies have accrued visceral adiposity in utero (Figures 4 and 5).⁷ Diabetes begets diabetes: If this baby starts out fat,



Figure 4. Normal weight baby (left) and an overweight baby (right).

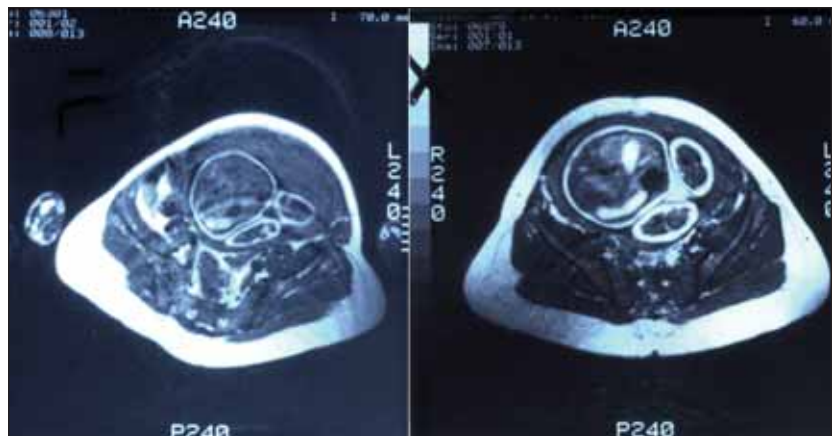


Figure 5. Overweight babies (right) have accrued adiposity in utero, compared with normal-weight babies (left).

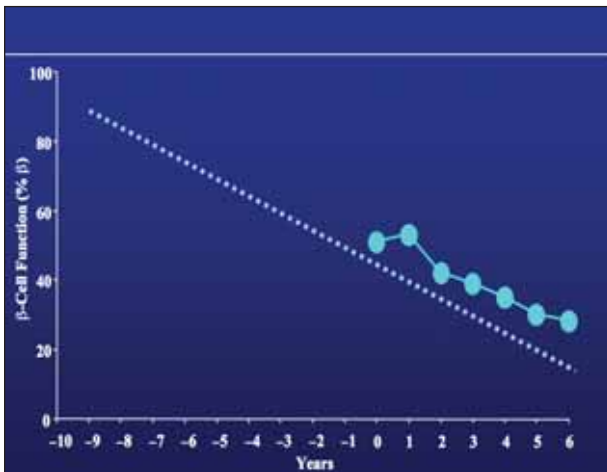


Figure 6. In the UKPDS when the diagnosis of diabetes was made at a much higher cutoff, patients had only 50% beta-cell function at time point zero.

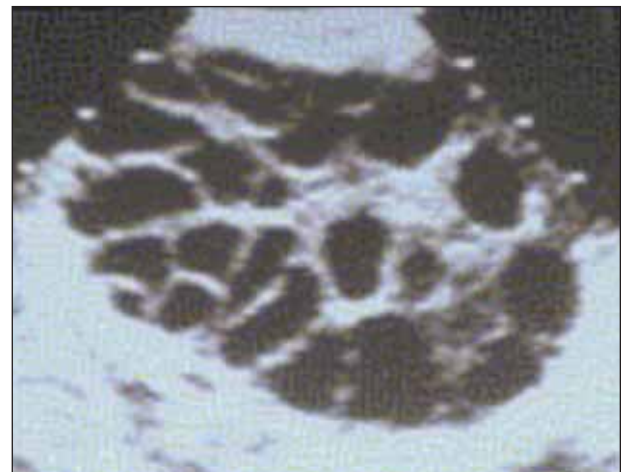


Figure 7. The ovary will attempt to increase ovulation, but the thickened theca will prevent eggs from being released, causing cysts.

what chance does it have to not develop problems as it grows and develops?

A normal islet has two phase of insulin secretion. The first phase of insulin response is the first squirt of insulin into the bloodstream, which compensates for the simple carbohydrates in our meal. The only way a normal islet can have enough insulin to be secreted the moment we eat a simple carbohydrate is to have rest, and it must store granules. If it is always secreting, it will exhaust the stores and will never rest. The second phase of insulin response is due to de novo production of insulin to perfectly compensate for the slower carbohydrates coming into our system.

Type 2 diabetes and gestational diabetes are the victims of no stored granules. The pancreas becomes exhausted and overworked and releases all of its stores of granules because of overeating. In these patients, the first phase of insulin secretion is lost. The pancreas overcompensates by increasing insulin secretion during the second phase. This high level of insulin in the bloodstream makes these people hungry again.

FIRST-PHASE LOSS HAPPENS EARLY

First phase loss of insulin secretion happens very early in glucose intolerance, and in fact, it happens even in obesity with a normal glucose tolerance. In addition to covering simple carbohydrates, the first phase of insulin secretion turns off glucagons, which turns off the liver production of glucose and keeps blood sugar normal. When we exhaust our secretory granules, by the time an islet makes new insulin and

it gets into the bloodstream, the food is gone.

In the United Kingdom Prospective Diabetes Study (UKPDS), when the diagnosis of diabetes was made at a much higher cutoff, patients had only 50% beta-cell function at time point zero (Figure 6).⁸ The ADA now realizes that we should make the diabetes diagnosis much earlier. In my opinion, the diagnosis is still made too late for many of our young women in childbearing years.

Too much insulin is also irritating to the skin and the ovaries. The outer lining of the ovary, called the *theca*, becomes thickened from too much insulin. This causes excess amounts of androgens to be produced, leading to problems such as acne, hirsutism, alopecia and increased muscle mass. Hyperinsulinemia will also force the pituitary gland to overproduce luteinizing hormone (LH). The ovary will attempt to increase

Type 2 Diabetes Prevention					
	Study	Subjects	Intervention	Rel. Risk Reduction	Abs. Risk Reduction
Behavior	Finnish DPS	I.G.T.	Diet+Exercise	58%	22%
	U.S.DPP	I.G.T.	Diet+Exercise	58%	17%
Medication	TRIPOD	Prior GDM	Troglitazone	55%	31%
	U.S. DPP	I.G.T.	Metformin	31%	8%
	Stop-NIDDM	I.G.T.	Acarbose	25%	7%

Figure 8. Keeping women lean and fit can reduce their risk of developing type 2 diabetes from >50% to <20%.

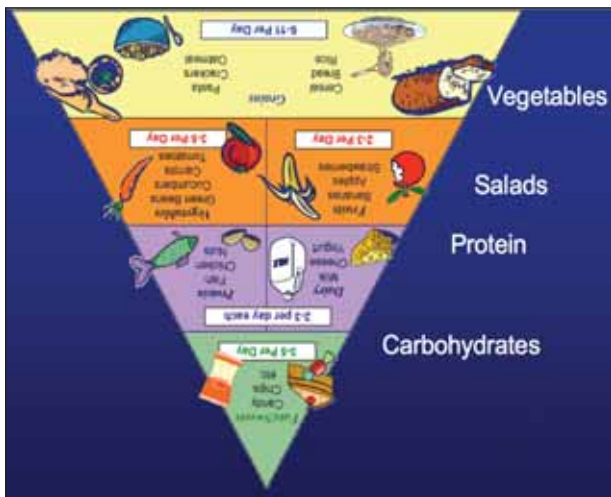


Figure 9. The food pyramid should stand on its head.

ovulation, but the thickened theca will prevent eggs from being released, and it may cause cysts (Figure 7). PCOS is really a misnomer — the ovary is only the end stage of the disease. The term *hyperthecosis syndrome* is more accurate:

- PCOS exists in 5% to 10% of all obese women;
- 50% to 76% of women with PCOS will develop gestational diabetes;
- 25% of women with gestational diabetes also have PCOS;
- Decreasing insulin concentrations will cure the syndrome; and
- 5% to 10% of women with PCOS are not obese.

Ehrmann and colleagues in a *New England Journal of Medicine* article developed a diagnostic algorithm for PCOS.⁹ It is easy to diagnose; certain syndromes must be ruled out. Laboratory data that should be used to diagnose PCOS include:

- fasting insulin value >20 mIU/mL;
- fasting glucose >95 mg/dL;
- testosterone >40 ng/dL; and
- LH:FSH ratio >3 (only in patients with a BMI ≤ 27).

LIFESTYLE INTERVENTIONS

Can lifestyle intervention and prevention stop the cascade of events that leads to PCOS? Plenty of studies show that keeping women lean and fit can reduce their risk of developing type 2 diabetes from >50% to <20% (Figure 8). If this problem is due to overnutrition, then why not teach programs of caloric and carbohydrate restriction when people are young and healthy? Because people of different ages have differing caloric requirements. While very active women, pregnant and lactating women can increase calories, a

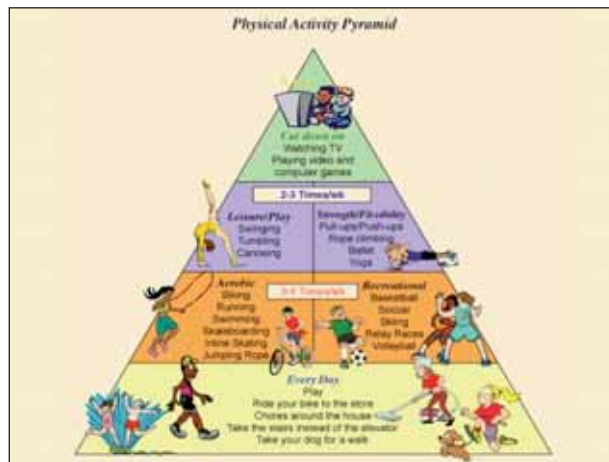


Figure 10. The food pyramid should stress exercise throughout the day.

pregnant woman still needs only half the calories of a man the same age.

We should pay attention to the types of calories that cause insulin levels to spike. Moran and coworkers¹⁰ conducted a study in a population of overweight women with PCOS and calorically restricted them. The women were restricted to 600 calories/day for 12 weeks and randomized to a diet of 40% carbohydrate and 30% protein or 55% carbohydrate and 15% protein. The women assigned to the 40% carbohydrate diet had significantly decreased insulin resistance and fasting insulin ($P=.011$). The other group had a 10% decrease in HDL cholesterol and their free androgen index increased 44% ($P=.008$).

The optimal diet to prevent hyperinsulinemia restricts carbohydrates, forbids simple sugars and emphasizes proteins.

In our own pregnancy studies, we have calculated the perfect postprandial blood sugar and extrapolated that to the carbohydrate content of the meal plan. We are restricting carbohydrate during pregnancy to keep the peak at 120 mg/dL so the baby does not become over-nourished.

OPTIMAL DIET RESTRICTS CARBS

The optimal diet to prevent hyperinsulinemia restricts carbohydrates. Simple sugars are forbidden, as are seven fruits (ie, oranges, cherries, melons, bananas,

grapes, mangoes and berries) and five complex carbohydrates and starches (ie, tortillas or pasta, rice, bread, potatoes and cereal). Proteins, such as fish, poultry, eggs, dairy and pork are emphasized — not only should the pyramid stand on its head (Figure 9), it should also stress exercise throughout the day so that we burn calories as we eat them (Figure 10).

In addition to treating PCOS with carbohydrate restriction, effective drug treatments are available,⁹ including metformin. Women with PCOS, however, are at an increased risk for spontaneous abortion, and metformin crosses the placenta. A literature review conducted prior to 2001 reveals that if women stop metformin after conception, they have a 40% to 60% risk of spontaneous abortion. If they continue to take metformin during the first trimester, their risk decreases to 20%. There was, however, no documentation of maternal glycemia in these studies.

Empirically, then, many gynecologists use progesterone in the first trimester in cases of recurrent spontaneous abortion. Thus, women are essentially hormonally equivalent to a second trimester when placental progesterone is high enough to cause glucose intolerance. Gynecologists often use metformin as well, but glucose intolerance may have developed despite its use.

SYNTHESIZING THE DATA

Normal healthy women have a spontaneous abortion rate of about 16%; women with HbA1c two standard deviations above the mean start at a rate of 16%, but this increases rapidly as HbA1c rises. Glucose is toxic, causing malformations and spontaneous abortion.

By bringing blood sugars down even lower, we can bring the spontaneous abortion rate in women with diabetes down to 9%.

Glueck and colleagues¹¹⁻¹³ confirmed that women on metformin had a 20% spontaneous abortion rate; without metformin, this rate is 60% in a diagnosis of gestational diabetes. Other common causes of spontaneous abortions are a clotting or immunologic defect and gene mutation (factor V Leiden, 4G4G PAI-1 gene mutation). This defect in the clotting cascade can be measured and treated with low-molecular weight heparin (LMWH).

In summary, evidence-based medicine has to be conducted. In the absence of that, we have expert opinions. My 10 Commandments are:

1. Make the diagnosis (ICD-9 620.2).
2. Make the diagnosis and treat diabetes, thrombophilia/hypofibrinolysis.
3. Initiate diet and exercise.

4. Treat with high-dose metformin for 4 to 6 months (if periods do not normalize, add clomiphene).

5. Measure human chorionic gonadotropic 1 day after missed period.

6. Stop metformin.

7. Begin self-monitored blood glucose, fasting and 1 hour after meals.

8. Begin insulin (if fasting levels are >90 mg/dL and/or 1-hour levels are >120 mg/dL).

9. Remeasure markers of thrombophilia/hypofibrinolysis.

10. Continue or start therapy with aspirin or LMWH.

Eight percent of women with PCOS conceive after taking high-dose metformin for 4 to 6 months. I am convinced that a normal blood sugar level for women of all ages and stages of life will make them healthy and the next generation healthy, too. ■

Lois Jovanovic, MD, is CEO and chief scientific officer of Sansum Diabetes Research Institute in Santa Barbara, Calif. Dr. Jovanovic is also clinical professor of medicine at the University of Southern California-Los Angeles Medical Center. She may be reached at ljovanovic@sansum.org.

1. Jovanovic L. PCOS diagnosis and treatment with an eye towards pregnancy. Presented at the American Association of Diabetes Educators 33rd Annual Meeting & Exposition. Aug 9-12, 2006. Los Angeles.
2. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med.* 1995;122:481-486.
3. Buchanan TA. Diabetes In America, 2nd edition. 1995. National Diabetes Data Group. National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases. NIH Publication No. 95-1468;chap 36.
4. Pierce J. California Dept of Health Services. 1993. Maternal and Child Health Branch. #89-97644.
5. Proceedings of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care.* 1998;21;(Suppl 2).
6. Jovanovic-Peterson L, Peterson CM, Reed GF, et al. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol.* 1991;164:103-111.
7. Jovanovic-Peterson L, Crues J, Durak E, Peterson CM. Magnetic resonance imaging in pregnancies complicated by diabetes predicts infant birthweight ratio and neonatal morbidity. *Am J Perinatol.* 1993;10:432-437.
8. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type 2 diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes.* 1995;44:1249-1258.
9. Ehrmann DA. Medical progress: Polycystic ovary syndrome. *N Engl J Med.* 2005;352:1223-1236.
10. Moran LJ, Noakes M, Clifton PM, et al. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2003 88:812-819.
11. Glueck CJ, Wang P, Goldenberg N, Sieve L. Pregnancy loss, polycystic ovary syndrome, thrombophilia, hypofibrinolysis, enoxaparin, metformin. *Clin Appl Thromb Hemost.* 2004;10:323-334.
12. Glueck CJ et al Metabolism. Polycystic ovary syndrome, the G1691A factor V Leiden mutation, and plasminogen activator inhibitor activity: associations with recurrent pregnancy loss. *Metabolism.* 2003;52:1627-1632.
13. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod.* 2002;17:2858-2864.