In Brief

Diabetes during pregnancy is a major risk factor for poor fetal, neonatal, and maternal outcomes; however, the risk can be greatly reduced by early institution of medical nutritional therapy and insulin treatment. Maintaining maternal glycemia as near to normal as possible reduces the risk of congenital anomalies, macrosomia, neonatal hypoglycemia, and large-for-gestational-age infants. Achieving normoglycemia has usually been accomplished with human insulin. However, the newer rapid-acting insulin analogs lispro and aspart, when compared to regular human insulin, demonstrate both efficacy and safety for the treatment of diabetes during pregnancy. NPH insulin is the only basal insulin that has been studied in pregnancy. There are not yet any published controlled studies evaluating the long-acting insulin analogs for use in pregnancy.

Insulin Analogs and Pregnancy

Angelina L. Trujillo, MD, FACE

Pregnancy complicated by diabetes occurs in ~ 4% of pregnancies in the United States.[1] With appropriate institution of intensive diabetes therapy and maintenance of glucose levels to achieve a lowering of hemoglobin A_{1c} (A1C) levels before and during pregnancy complicated by diabetes, the rate of fetal and maternal complications can be reduced to the rate observed among nondiabetic pregnancies.[2] Whether the pregnancy is classified as pregestational diabetes (occurring in women who have been diagnosed with type 1 or type 2 diabetes before pregnancy) or as gestational diabetes mellitus (GDM, occurring when a nondiabetic woman develops diabetes only during pregnancy), the goal of treatment is to maintain maternal glucose levels as near to normal as possible throughout the pregnancy.

Pregestational diabetes is a major risk factor for spontaneous abortions and congenital malformations, but the risk can be significantly reduced when hyperglycemia is controlled before conception and during the early first trimester when fetal organogenesis occurs.[3,4] In both pregestational diabetes and GDM, achieving near-normal glycemic levels throughout pregnancy can also decrease the prevalence of neonatal hypoglycemia, macrosomia, intrauterine death, and cesarean delivery.[5–7] Achieving near-normal glycemia means normalizing not only fasting glucose, but also postprandial hyperglycemia to reduce the risk of an adverse pregnancy outcome.[8–10] The infant mortality rate is nearly zero when blood glucose concentration is maintained at near-normoglycemia.[11] In both type 1 and type 2 diabetes, controlling pre- and postprandial hyperglycemia can best be accomplished during pregnancy by administering insulin via continuous subcutaneous insulin infusion from an insulin pump or by self-administration of multiple daily injections of an intermediate-acting basal human insulin (neutral protamine Hagedorn [NPH] insulin) combined with a short-acting or rapid-acting insulin. In GDM, achieving normoglycemia can initially be attempted with medical nutrition therapy and lifestyle modifications, but frequently, NPH insulin combined with a short-acting or rapid-acting insulin must be added to attain optimal glucose levels.

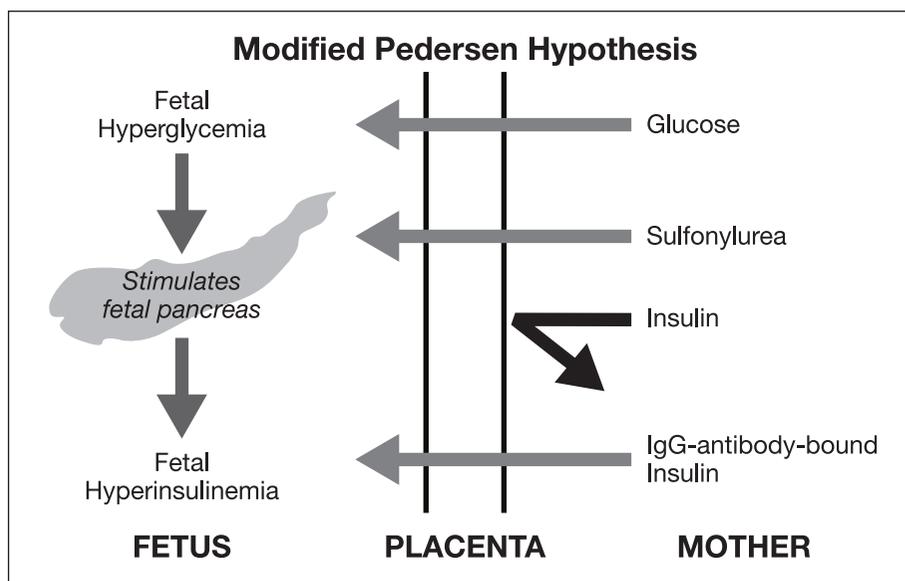Throughout pregnancy, the placenta not only produces hormones that alter

Modified Pedersen Hypothesis

Figure 1. Development of fetal hyperinsulinemia. Adapted from Ref. 15.

Table 1. Calculation of Insulin Dosing

- Woman's weight in pounds ÷ 2.2 = woman's weight in kilograms

- Weight in kilograms × k = total insulin requirement
  → k = 0.7, 0.8, and 0.9 for first, second, and third trimesters, respectively

- 50% of total insulin requirement = daily basal insulin dosage provided by long-acting insulin
  → Administered before breakfast (8:00 A.M.), before supper (4:00 P.M.), and at midnight

- 50% of total insulin requirement = daily bolus insulin dosage provided by rapid-acting insulin
  → Administered before breakfast (8:00 A.M.), before lunch (noon), and before supper (4:00 P.M.)

Adapted from Ref. 18.

maternal carbohydrate and lipid metabolism, but it also controls the transplacental passage of glucose, fat, and protein to provide fuel energy and nutrients to the developing fetus. Maternal insulin is not transferred across the placenta unless the insulin is bound to IgG antibodies.[12,13] A study by Balsells et al.[14] evaluated 50 women with GDM before and after treatment with human insulin, which is immunogenic, and found that 44% developed insulin antibodies. They also found that cord blood titers at delivery reflected the maternal antibody levels, indicating transplacental passage of human insulin when bound with maternal antibodies. In the same study, the status of the maternal insulin antibody did not appear to have an impact on fetal outcome.

Because of the facilitated diffusion of glucose across the placenta, the maternal glucose level determines the glucose level of the fetus. When the maternal glucose level is high, the fetus becomes hyperglycemic, resulting in stimulation of the fetal pancreas to produce high levels of insulin (Figure 1).[15]

Because insulin is a growth factor, the high fetal insulin level increases intrauterine fetal growth, producing a newborn that is large for gestational age (LGA; weight > 90th percentile) or has macrosomia (weight > 4,000 g).[16] Both conditions are frequently associated with birth trauma, especially shoulder dystocia, which occurs in 0.6–1.4% of fetuses weighing 2,500–4,000 g and in 5–9% of fetuses weighing > 4,000 g.[17] Fetal hyperinsu-

linemia can also produce neonatal hypoglycemia after the infant is delivered and is no longer exposed to maternal hyperglycemia. Treatment of diabetic pregnant women with insulin to maintain maternal glucose levels near normal will prevent the development of fetal hyperinsulinemia in utero and decrease the risk of adverse fetal or neonatal outcomes associated with excess fetal growth.

The insulin requirement necessary to achieve near-normal maternal glycemia is based on the patient's weight and the number of weeks of gestation (Table 1).[18]

In recent years, molecularly engineered insulin analogs (the "new" insulins) have been developed and become available for the treatment of patients with hyperglycemia and diabetes.

The currently available rapid-acting insulin analogs are lispro, aspart, and glulisine; the long-acting insulin analogs are glargine and detemir. Lispro, aspart, and glulisine are similar rapid-acting formulations used primarily for mealtime insulin requirements, whereas glargine and detemir are long-acting basal formulations.[19–21] Also available are two biphasic formulations: biphasic aspart, which is a mixture of 30% aspart with 70% protaminated aspart, and biphasic lispro either consisting of 25% lispro and 75% protaminated lispro or 50% lispro and 50% protaminated lispro.

The insulin analogs are produced by recombinant DNA methods. Lispro, prepared by *E. coli*, differs from human insulin by two amino acid substitutions on the insulin β-chain; a lysine is substituted at position 28 and a proline at position 29, both of which are the reverse of human insulin. Aspart uses *saccharomyces cerevisiae* (yeast) to replace the proline at position 28 with an aspartic acid. Glulisine also has a double substitution, replacing asparagine with lysine at position 3 and lysine with glutamic acid at position 29. These modifications of the insulin β-chain inhibit the self-aggregation of insulin to form dimers and hexamers, resulting in monomers that are rapidly absorbed when administered subcutaneously and thus allowing a faster onset of action.

Glargine was the first long-acting analog to become commercially available. It has a glycine substituted for asparagine at position 21 on the insulin α-chain and two arginines

Table 2. Insulin and Insulin Analogs

Insulin	Onset of action (minutes)	Time to peak concentration (minutes)	Maximum duration of action (hours)
Regular insulin	30–60	90–120	5–12
Insulin lispro (Humalog)	10–15	30–60	3–4
Insulin aspart	10–15	40–50	3–5
Insulin glulisine	10–15	55	3–5
NPH insulin	60–120	240–480	10–20
Insulin glargine	60–120	None	24
Insulin detemir	60–120	None	20

Adapted from Refs. 19 and 20.

Table 3. Current Categories for Drug Use in Pregnancy as Assigned by the U.S. Food and Drug Administration

Category	Description
A	No increased risk of fetal abnormalities have been demonstrated in adequate, well-controlled studies in pregnant women.
B	There are no adequate and well-controlled studies in pregnant women; however, animal studies have not revealed evidence of harm to the fetus.
C	There are no adequate and well-controlled studies in pregnant women; however, an adverse effect has been shown in animal studies. *-or-* Adequate and well-controlled studies in pregnant women have failed to show a risk to the fetus; however, an adverse effect has been shown in animal studies.
D	A risk to the fetus has been demonstrated in adequate, well-controlled or observational studies in pregnant women; however, the benefits of therapy may outweigh the potential risk.
X	Positive evidence of fetal abnormalities has been demonstrated in adequate well-controlled or observational studies in pregnant women or in animals. Therefore, the use of the product is contraindicated in women who are or may become pregnant.

Adapted from Ref. 36.

added to the carboxyl terminal of the β-chain at positions 31 and 32. These amino acid modifications shift the isoelectric point of the insulin molecule from a pH of 5.4 toward a neutral pH, which delays its absorption and prolongs the duration of action.

Detemir is produced by the elimination of threonine at position 30 and the addition of myristic acid, a 14-carbon fatty acid chain, to the lysine located at position 29 of the β-chain. This acylation results in increased self-aggregation and greater reversible albumin binding that prolongs absorption to reach a maximum concentration in 6–8 hours and prolongs the duration of action up to 24 hours.

Rapid-Acting Insulin Analogs
Compared with regular insulin, the rapid-acting insulin analogs have a more rapid onset of action as well as a more rapid decline in concentration, which is advantageous for reducing postprandial hyperglycemia while avoiding late hypoglycemic events (Table 2).

Lispro, with an onset of action within 10–15 minutes, reaches peak concentration within 30–60 minutes and has a duration of action up to 3–4 hours.[20] Aspart is similar to lispro but may have a slightly longer time to peak concentration (40–50 minutes) as well as a slightly longer duration of action (3–5 hours).[22] Glulisine also has a similar onset and duration of action, but has a slightly longer time to reach peak concentration (55 minutes).[23] Overall, when administered subcutaneously, the rapid-acting insulin analogs appear to have very similar pharmacodynamic and pharmacokinetic profiles.[24–26] Compared with regular human insulin, which has an onset of action of 30–45 minutes and a relatively prolonged effect of 2–3 hours, the rapid-acting insulin analogs have each demonstrated faster onset of action, earlier peak concentration, and briefer duration of action to achieve a more physiological dosing of insulin for lowering of prandial hyperglycemia while avoiding late-onset hypoglycemia.[27]

Long-Acting Insulin Analogs
Glargine has a longer time to onset of action (1.5 hours) compared to NPH (0.8 hour) and ultralente insulin (1 hour), whereas the duration of action of glargine is longer (20.5 hours) than that of NPH (13.2 hours) and is similar to that of ultralente (19 hours) (Table 2).[28] Ultralente insulin is no longer available. In addition, several studies have reported less nocturnal hypoglycemia in both type 1 and type 2 diabetes, and in type 2 diabetes, there has been less weight gain with glargine than with NPH.[29–31]

Detemir appears to have a similar profile to glargine, with slow absorption of 3–4 hours and a prolonged effect up to 24 hours[32,33] (Table 2); however, the best profiles are achieved when the insulin is administered twice daily. In clinical studies, detemir also demonstrated lower risk of nocturnal hypoglycemia and less weight gain compared to NPH in type 1 diabetes.[33–35]

The long-acting insulin analogs, when used in nonpregnant patients with diabetes, appear to be most useful as basal insulin because of their long duration and lack of a peak.

Efficacy and Safety of Insulin Analogs During Pregnancy
All of the insulin analogs have been assigned a "safety during pregnancy" risk factor by the U.S. Food and Drug Administration (Table 3).[36] Lispro and

aspart are the only insulin analogs currently classified as pregnancy risk Category B, which is the same risk category as regular insulin.

The benefit of controlling maternal glycemia during pregnancy by reducing hyperglycemia and avoiding hypoglycemia has been well documented.[2,3,37] Until the introduction of the insulin analogs, glycemic control during pregnancy was usually managed with diet and human insulin.

Lispro has been the most well studied during pregnancy. In pregnant women with type 1 diabetes, lispro has been shown to reduce A1C levels and postprandial glucose levels to lower or similar levels as those achieved with regular insulin but with fewer severe hypoglycemic events than with regular insulin.[38–43] Similar findings have been reported for aspart in the treatment of GDM when compared to regular insulin.[44,45] From these data, lispro and aspart appear to be as efficacious as regular insulin for improving glucose control while avoiding late hypoglycemic events during management of pregnancy complicated by diabetes. At present, there are no studies evaluating the use of glulisine during pregnancy.

There have been no comparator-controlled studies using the long-acting insulin analogs during pregnancy; however, there have been several case reports in which glargine was used for the treatment of hyperglycemia during pregnancy. These reports suggest that, compared to NPH, glargine results in improved glycemic control without any nocturnal hypoglycemia.[46–48]

Although the insulin analogs appear to be effective and efficacious for controlling maternal hyperglycemia, there have been several concerns regarding their safety during pregnancy.

Safety of Insulin Analogs
Retinopathy and analogs. During the early weeks of pregnancy, women with the greatest decrease in A1C have an increased risk for progression of retinopathy. Reports early in the clinical use of lispro proposed that this insulin analog had a potential risk for developing or exacerbating diabetic retinopathy during pregnancy. These reports were based on the greater homology of lispro with insulin-like growth factor 1 (IGF-1), a growth hormone that has been indirectly implicated in the development of retinopathy

among insulin-treated patients with type 1 diabetes.[49,50] Because lispro binds more than insulin to the IGF-1 receptor, it was postulated in an initial report in 1999 that if a patient were treated with lispro during pregnancy, there was a potential risk for increasing the development of diabetic retinopathy.[49] The authors had reported on three pregnant women treated with lispro who progressed from no background retinopathy to bilateral proliferative diabetic retinopathy.[51] However, subsequent case reports comparing lispro to regular insulin have clearly shown that the incidence for progression of retinopathy is no different with lispro than with regular insulin.[52,53] Table 4 summarizes the results of studies evaluating retinopathy compared to regular insulin in pregnant women with type 1 diabetes, type 2 diabetes, or GDM.

Congenital anomalies and analogs. The increased potential for congenital malformations resulting from lispro has also been considered. However, when outcomes of lispro treatment during pregnancy were compared to those of pregnant women treated with regular insulin, there was no increased

Table 4. Retinopathy and Rapid-Acting Insulin Analogs in Pregnancy

Studies	n	Type of diabetes	Insulin				Outcome
			Lispro	Aspart	Regular Human	Animal	
Kitzmiller et al.[51]	14	Type 1 and 2	14				3 progressed from no background DR to bilateral PDR including 2 vitreous hemorrhages
Bhattacharyya et al.[52]	40	27 with type 1 and 3 with type 2	16		21	3	No progression of retinopathy from baseline
Buchbinder et al.[53]	54	Type 1	12		42		No progression in the lispro group; 6 progressed in the regular insulin group
Persson et al.[41]	33	Type 1	16	0	17		No difference in progression of DR in both groups; lispro = 3/16; regular = 6/17 with 1 PDR
Masson et al.[42]	76	Type 1	76	0	0		None without DR at baseline progressed to DR; 6 with DR at baseline required laser therapy for PDR
Loukovaara et al.[43]	72	Type 1	37		35		2 lispro patients developed bilateral PDR during pregnancy; 2 regular insulin patients developed PDR postpartum
Jovanovic et al.[38]	42	GDM	19	0	23		No differences in maternal, fetal, or neonatal outcomes

DR, diabetic retinopathy; PDR, proliferative diabetes retinopathy.

Table 5. Congenital Anomalies Among Pregnancies Treated With Rapid-Acting Insulin Analogs

Studies	n	Type of diabetes	Diet	Insulin Lispro	Insulin Regular human	Outcome
Bhattacharyya et al.[39]	619	81 had type 1 or type 2; 538 had GDM	323	101	195	Diet-treated 5.2% had Down's, hydronephrosis, or ventricular septal defect; regular insulin-treated 7.9% had tetralogy, hydronephrosis, or ambiguous genitalia; lispro-treated 6.6% had meningo-myelocoele
Masson et al.[42]	76	Type 1		76	0	4 CM: 1 Down's syndrome, 1 systolic murmur, 1 deformed hand with absent radius, and 1 polydactyly
Diamond and Kormas[54]	2	Type 1?		2		Patient 1: TAB at 20 weeks' gestation for embryopathy, multiple fetal abnormalities Patient 2: Infant deceased at 3 weeks of age; Diaphragmatic hernia into chest and bilateral undescended testes
Idama et al.[55]	7	Type 1		7		No congenital abnormalities
Scherbaum et al.[56]	60	Type 1?		33	27	Lispro-treated: 1 SAB, 1 TAB due to multiple malformations; 1 heart malformation; 1 hyaline membrane syndrome Regular insulin–treated: 1 dysplastic hip

CM, congenital malformations; SAB, spontaneous abortion; TAB, therapeutic abortion.

Table 6. Neonatal Macrosomia During Pregnancy Treated With Lispro

Studies	Pregnancies (n)	Type of diabetes	Nondiabetic	Insulin Lispro	Insulin Regular	Outcome
Evers et al.[60]	289	Type 1		11		Increased frequency of macrosomia with lispro
Ozcan et al.[59]	50	GDM		21	29	Less frequent macrosomia with lispro
Mecacci et al.[40]	49	GDM	50	25	24	No increased frequency of macrosomia with lispro

CM, congenital malformations; SAB, spontaneous abortion; TAB, therapeutic abortion.

incidence of congenital anomalies among neonates whose mothers had been treated with lispro during gestation (Table 5).[39,41,42]

Macrosomia and analogs. Placental transfer of insulin can occur when insulin becomes bound with immunoglobulin,[13,57] thereby contributing to excess fetal growth and development of macrosomia. In addition, lispro has not been detected in cord blood at delivery.[58] A study by Jovanovic et al.[38] compared 19 women with GDM treated with lispro with 22 women with GDM treated with human regular insulin. Although anti-insulin antibodies were similar in the two maternal groups, lispro was nondetectable in the cord blood, suggesting that it does not cross the placenta. In addition, no

fetal or neonatal abnormalities were identified in either group.

The studies in Table 6 have evaluated the incidence of neonatal macrosomia among women treated with lispro compared with human regular insulin.

There are no controlled human studies of glargine use during pregnancy. The effect of glargine in pregnancy has only been evaluated in animal studies in which toxicological effects were seen at doses that were seven times the highest human dose of both glargine and NPH insulin.[61] These effects resulted from the hypoglycemia that both insulins induced. There appeared to be no effect on reproduction or embryo-fetal development among the studies conducted in rats.[61] In addition, it is not known whether

glargine is excreted in breast milk. However, because human insulin is excreted in human milk, caution has been recommended for nursing mothers who are using glargine.[62]

There have been many case reports in which pregnant women with diabetes were treated with glargine. Table 7 summarizes the outcomes of those reports. Although glargine may improve control compared to NPH, it is not possible to determine the frequency of macrosomia from these reports.

There have been no clinical trials in human pregnancy treated with detemir, the other long-acting insulin analog, although clinical trials are in the early stages. Animal studies for embryotoxicity and teratogenicity have not demonstrated any difference

Table 7. Use of Long-Acting Insulin Glargine in Pregnancy

Studies	n	Type of diabetes	Treatment with glargine	Outcome
Woolderink et al.[64]	7	Type 1	5 treated throughout pregnancy; 2 began glargine in second trimester	Delivered at 37-40 weeks Birth weight 4,180 g (2,475–4,675 g) A1C 6.4% (5.2–8.1%) No congenital malformations
Graves et al.[65]	4	GDM	? trimester	1 LGA neonate 1 patient with daytime hypoglycemia No cases of nocturnal hypoglycemia
Dolci et al.[48]	1	Type 1 and Addison's disease	second trimester	Compared to NPH in first trimester, better control with glargine
Di Cianni et al.[63]	5	Type 1	first trimester	No congenital malformations
Devlin et al.[47]	1	Type 1	second and third trimester	Better glycemic control with glargine than NPH
Holstein et al.[46]	1	Type 1	first, second, and third trimester	Better glycemic control with glargine than NPH
Torlone et al.[21]	6	Type 1	first, second, and third trimester	Normal outcome
Carrona et al.[66]	1	Type 1	first, second, and third trimester	3,540-g male infant

CM, congenital malformations; SAB, spontaneous abortion; TAB, therapeutic abortion.

between detemir and NPH insulin. Although it is clear that human insulin and all of the rapid-acting insulin analogs appear in milk directly proportional to the serum levels of insulin or insulin analog achieved in the maternal bloodstream, it is currently unknown whether detemir is excreted in breast milk. Therefore, women who use detemir must also be cautioned when lactating.[67] However, since insulin is not absorbed through the gut, even if the insulin appears in human milk, it is not biologically active. Although glargine and detemir reportedly have been used during pregnancy, there is insufficient data to support their use as a safe basal insulin during pregnancy. Additional studies are needed to evaluate the efficacy and safety of glargine and detemir compared with the current use of NPH basal insulin during pregnancy complicated by diabetes.

Conclusions
For pregnant women with diabetes, the timely initiation of insulin treatment to maintain preprandial glucose levels < 90 mg/dl and postprandial glucose levels < 120 mg/dl has reduced the risks of fetal and maternal complications. When compared with human regular insulin, the rapid-acting insulin analogs have been shown to be efficacious in reducing hyperglycemia during pregnancy, with a safety profile that resulted in a lower incidence of neonatal complications. NPH insulin is the only

basal insulin that has been adequately studied in pregnancy. The long-acting insulin analogs do not yet have sufficient safety evaluation in clinical studies to warrant their use during pregnancy.

In addition to diet and lifestyle modifications, the treatment algorithm in Table 1 is the currently recommended guideline for all insulin-requiring pregnant women with type 2 diabetes or GDM or pregnant women with type 1 diabetes who require multiple daily insulin injections and are not using an insulin pump. Early and intensive treatment intervention will improve the outcome of all pregnancies complicated by diabetes.

References

[1]Engelgau MM, Herman WH, Smith PJ, German RR, Aubert RE: The epidemiology of diabetes and pregnancy in the U.S., 1988. *Diabetes Care* 18:1029–1033, 1995

[2]The DCCT Research Group: Pregnancy outcomes in the Diabetes Control and Complications Trial: *Am J Obstet Gynecol* 174:P1343–P1353, 1996

[3]Yang J, Cummings EA, O'Connel C, Jangaard K: Fetal and neonatal outcomes of diabetic pregnancies. *Obstet Gynecol* 108:644–650, 2006

[4]Ray JG, O'Brien TE, Chan WS: Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: a meta-analysis. *Q J Med* 94:435–444, 2001

[5]Kitzmiller JL, Gavin LA, Gin GD, Jovanovic-Peterson L, Main EK, Zigrang WD: Preconception care of diabetes: glycemic control prevents congenital anomalies. *JAMA* 265:731–736, 1991

[6]De Veciana MD, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, Evans AT: Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 333:1237–1241, 1995

[7]Walkinshaw SA: Pregnancy in women with pre-existing diabetes: management issues. *Sem Fetal Neonatal Med* 10:307–315, 2005

[8]Jovanovic-Peterson L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, Aarons JH: Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy study. *Am J Obstet Gynecol* 164:103–111, 1991

[9]Combs CA, Gunderson E, Kitzmiller JL, Gavin LA, Main EK: Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care* 15:1251–1257, 1992

[10]Manderson JG, Patterson CC, Hadden DR, Traub AI, Ennis C, McCance DR: Preprandial versus postprandial blood glucose monitoring in type 1 diabetic pregnancy: a randomized controlled clinical trial. *Am J Obstet Gynecol* 189:507–512, 2003

[11]Jovanovic L, Peterson CM, Saxena BB, Dawood MY, Saudek CD: Feasibility of maintaining normal glucose profiles in insulin-dependent pregnant diabetic women. *Am J Med* 68:105–112, 1980

[12]Buse MG, Roberts WJ, Buse J: The role of the human placenta in the transfer and metabolism of insulin. *J Clin Invest* 41:29–41, 1962

[13]Bauman WA, Yalow RS: Transplacental passage of insulin complexed to antibody. *Proc Natl Acad Sci U S A* 78:4588–4590, 1981

[14]Balsells M, Corcoy R, Mauricio D, Morales J, Garcia-Patterson A, Carreras G, Puig-Domingo M, de Leiva A: Insulin antibody response to a short course of human insulin therapy in women with gestational diabetes. *Diabetes Care* 20:1172–1175, 1997

[15]Pedersen J: Weight and length of infants of diabetic mothers. *Acta Endocrinol* 12:330–342, 1954

[16]Langer O: Fetal macrosomia: etiologic factors. *Clin Obstet Gynecol* 43:283–297, 2000

[17]Baxley EG, Gobbo RW: Shoulder dystocia. *Am Fam Phys* 69:1707–1714, 2004

[18]Gamson K, Chia S, Jovanovic L: Review the safety and efficacy of insulin analogs in pregnancy. *J Matern-Fetal Neonat Med* 15:26–34, 2004

[19]Drugs for Diabetes: Treatment Guidelines from the Medical Letter. 3:57–62, 2005

[20]Insulin detemir (Levemir), a new long-acting insulin. *Med Lett Drug Ther* 48:54–55, 2006

[21]Torlone E, Gennarini A, Ricci NB, Bolli GB: Successful use of insulin glargine during entire pregnancy until delivery in six type 1 diabetic women. *Eur J Obstet Gynecol Reprod Biol* 24 June 2006. Epub ahead of print

[22]Novolog insulin aspart (rDNA origin) injection prescribing information. Princeton, N.J., Novo Nordisk, Inc., 2007

[23]Apidra (insulin glulisine [rDNA origin] injection) prescribing information. Kansas City, Mo., Aventis Pharmaceuticals, 2005

[24]Hedman CA, Lindstrom T, Arnqvist HJ: Direct comparison of insulin lispro and aspart shows small differences in plasma insulin profiles after subcutaneous injection in type 1 diabetes. *Diabetes Care* 24:1120–1121, 2001

[25]Plank J, Wutte A, Brunner G, Siebenhofer A, Semlitsch B, Sommer R, Hirschberger S, Pieber TR: A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care* 25:2053–2057, 2002

[26]Homko C, Deluzio A, Jimenez C, Kolaczynski JW, Boden G: Comparison of insulin aspart and lispro pharmacokinetic and metabolic effects. *Diabetes Care* 26:2027–2031, 2003

[27]Taton J, Milicevik Z, Mozejko-Pastewka B, Bernas M, Czech A: How recombinant insulin analogs improve insulin therapy of diabetes mellitus: pathophysiology, clinical practice and recommendations. *Med Sci Monit* 7:848–859, 2001

[28]Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, De Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49:2142–2148, 2000

[29]Yki-Jarvinen H, Dressler A, Ziemen M, the HOE 901/3002 Study Group: Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 23:1130–1136, 2000

[30]Raskin P, Klaff L, Bergenstal R, Halle J-P, Donley D, Mecca T: A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care* 23:1666–1671, 2000

[31]Rosenstock J, Schwartz SL, Clark CM, Park GD, Donley DW, Edwards MB: Basal insulin therapy in type 2 diabetes 28-week comparison of insulin glargine (HOE 901) and NPH insulin.

Diabetes Care 24:631–636, 2001

[32]Plank J, Bodenlenz M, Sinner F, Magnes C, Gorzer E, Regittnig W, Endahl LA, Draeger E, Zdravkovic M, Pieber TR: A double-blind, randomized dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting analogue detemir. *Diabetes Care* 28:1107–1112, 2005

[33]Chapman TM, Perry CM: Spotlight on insulin detemir in type 1 and type 2 diabetes mellitus. *Bio Drugs* 19:67–69, 2005

[34]De Leeuw I, Vague P, Selam J-L, Skeie S, Lang H, Draeger E, Elte JWF: Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes Obes Metab* 7:73–81, 2005

[35]Kølendorf K, Ross GP, Pavlic-Renart I, Perriello G, Philotheous A, Jendle J, Gall M-A, Heller SR: Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in type 1 diabetes. *Diabet Med* 23:729–735, 2006

[36]Meadows M: Pregnancy and the drug dilemma. *FDA Consumer Magazine.* Washington, D.C., U.S. Food and Drug Administration, May-June 2001

[37]Jovanovic L, Knopp RH, Haesook K, Cefalu WT, Zhu X-D, Young JL, Simpson JL, Mills JL, for the Diabetes In Early Pregnancy Study Group: Elevated pregnancy losses at high and low extremes of maternal glucose in early normal and diabetic pregnancy: evidence for a protective adaptation in diabetes. *Diabetes Care* 29:113–117, 2005

[38]Jovanovic L, Ilic S, Pettitt DJ, Hugo K, Gutierrez M, Bowsher RR, Bastyr EJ: The metabolic and immunologic effects of insulin lispro in gestational diabetes. *Diabetes Care* 22:1422–1426, 1999

[39]Battacharyya A, Brown S, Hughes S, Vice PA: Insulin lispro and regular insulin in pregnancy. *Q J Med* 94:255–260, 2001

[40]Mecacci F, Carignani L, Cioni R, Bartoli E, Parretti E, La Torre P, Scarselli G, Mello G: Maternal metabolic control and perinatal outcome in women with gestational diabetes treated with regular or lispro insulin: comparison with non-diabetic pregnant women. *Euro J Obstet Gynecol Reprod Biol* 111:19–24, 2003

[41]Persson B, Swahn ML, Hjertberg R, Hanson U, Nord E, Nordlander E, Hansson LO: Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus. *Diabetes Res Clin Pract* 58:115–121, 2002

[42]Masson EA, Patmore JE, Brash PD, Baxter M, Caldwell G, Gallen IW, Price PA, Vice PA, Walker JD, Lindow SW: Pregnancy outcome in type 1 diabetes mellitus treated with insulin lispro (Humalog). *Diabet Med* 20:46–50, 2003

[43]Loukovaara S, Immonen I, Teramo KA, Kaaja R: Progression of retinopathy during pregnancy in type 1 diabetic women treated with insulin lispro. *Diabetes Care* 26:1193–1198, 2003

[44]Cypryk K, Sobczak M, Pertynska-Marczewska M, Zawodniak-Szalapska M, Szymczak W, Wilczynski J, Lewinski A: Pregnancy complications and perinatal outcome in diabetic women treated with Humalog (insulin lispro) or regular human insulin during pregnancy. *Med Sci Monit* 10:129–132, 2004

[45]Pettitt DJ, Ospina P, Kolaczynski J, Jovanovic L: Comparison of an insulin analogue, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care* 26:183–186, 2003

[46]Holstein A, Plaschke A, Egberts EH: Use of insulin glargine during embryogenesis in a pregnant woman with type 1 diabetes. *Diabet Med* 20:779–780, 2003

[47]Devlin JT, Hothersall L, Wilkis JL: Use of insulin glargine during pregnancy in a type 1 diabetic woman. *Diabetes Care* 25:1095–1096, 2002

[48]Dolci M, Mori M, Baccetti F: Use of glargine insulin before and during pregnancy in a woman with type 1 diabetes and Addison's disease. *Diabetes Care* 28:2084–2085, 2005

[49]DiMarchi RD, Chance RF, Long HB, Shields JE, Slieker LJ: Preparation of an insulin with improved pharmacokinetics relative to human insulin through consideration of structural homology with insulin-like growth factor I. *Horm Res* 41 (Suppl. 2):93–96, 1994

[50]Janssen JA, Jacobs ML, Derkx FH, Weber RF, van der Lely AJ, Lamberts SW: Free and total IGF-I, IGFBP-I and IGFBP-3 and their relationships to the presence of diabetic retinopathy and glomerular hyperfiltration in insulin-dependent diabetes mellitus (IDDM). *J Clin Endocrinol Metab* 83:2809–2815, 1997

[51]Kitzmiller JL, Main E, Ward B, Theiss T, Peterson DL: Insulin lispro and the development of proliferative diabetic retinopathy during pregnancy. *Diabetes Care* 22:874–875, 1999

[52]Bhattacharyya A, Vice PA: Insulin lispro, pregnancy and retinopathy. *Diabetes Care* 22:2101–2102, 1999

[53]Buchbinder A, Miodovnik M, McElvy S, Rosenn B, Kranias G, Khoury J, Siddiqi TA: Is insulin lispro associated with the development or progression of diabetic retinopathy during pregnancy? *Am J Obstet Gynecol* 183:1162–1165, 2000

[54]Diamond T, Kormas N: Possible adverse fetal effect of insulin lispro. *N Engl J Med* 337:1009–1010, 1997

[55]Idama TO, Lindow SW, French M, Massono EA: Preliminary experience with the use of insulin lispro in pregnant diabetic women. *J Obstet Gynecol* 21:350–351, 2001

[56]Scherbaum WA, Lankisch MR, Pawlowski B, Somville T: Insulin lispro in pregnancy: retrospective analysis of 33 cases and matched controls. *Exp Clin Endocrinol Diabetes* 110:6–9, 2002

[57]Menon RK, Cohen RM, Sperling MA, Cutfield WS, Mimouni F, Khoury JC: Transplacental passage of insulin in pregnant women with insulin-dependent diabetes mellitus: its role in fetal macrosomia. *N Engl J Med* 323:309–315, 1990

[58]Boskovic R, Feig DS, Derewlany L, Knie B, Portnoi G, Koren G: Transfer of insulin lispro across the human placenta. *Diabetes Care* 26:1390–1394, 2003

[59]Ozcan T, Karne A, Murphy J, Nickless N, Magriples U, Jones DC: Does lispro improve blood glucose control and birth weight? [Abstract] *Obstet Gynecol* 97:S41, 2001

[60]Evers IM, De Valk HW, Mol BWJ, Ter Braak EWMT, Visser GHA: Macrosomia despite good glycaemic control in type 1 diabetic pregnancy: results of a nationwide study in the Netherlands.

Diabetologia 45:1484–1489, 2002

[61]Hofmann T, Horstmann G, Stammberger I: Evaluation of the reproductive toxicity and embryotoxicity of insulin glargine (Lantus) in rats and rabbits. *Int J Toxicol* 21:181–189, 2002

[62]Lantus (insulin glargine [rDNA origin] injection) product information. Bridgewater, N.J., Sanofi-Aventis U.S., 2006

[63]Di Cianni G, Volpe L, Lencioni C, Chatzianagnostou K, Cuccuru I, Ghio A, Benzi L, Del Prato S: Use of insulin glargine during the first weeks of pregnancy in five type 1 diabetic women. *Diabetes Care* 28:982–983, 2005

[64]Woolderink JM, van Loon AJ, Storms F, De Heide L, Hoogenberg K: Use of insulin glargine during pregnancy in seven type 1 diabetic women. *Diabetes Care* 28:2394–2395, 2005

[65]Graves DE, White JC, Kirk JK: The use of insulin glargine with gestational diabetes mellitus. *Diabetes Care* 29:471–472, 2006

[66]Caronna S, Cioni F, Dall'aglio E, Arsenio L: Pregnancy and the long-acting insulin analogue: a case study. *Acta Biomed Ateneo Parmense* 77:24–26, 2006

[67]Levemir (insulin detemir [rDNA origin] injection) prescribing information. Bagsvaerd, Denmark, Novo Nordisk A/S, 2005

Angelina L. Trujillo, MD, is an internal medicine and endocrinology specialist and a senior scientist at the Sansum Diabetes Research Institute in Santa Barbara, Calif.