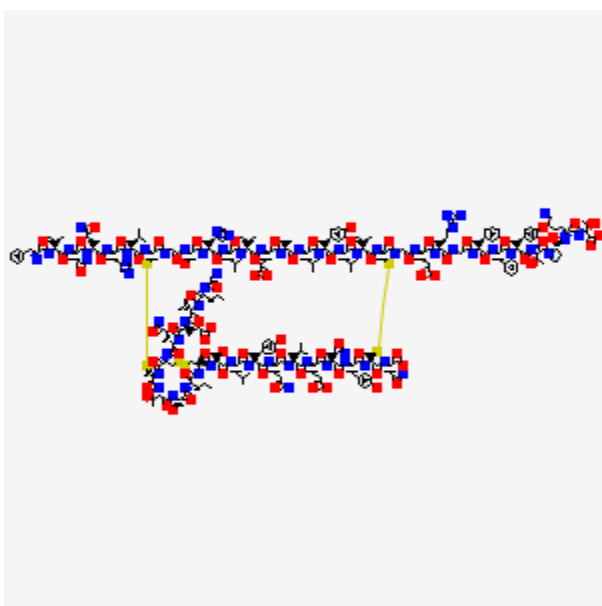




Insulin

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Drug Levels and Effects

Summary of Use during Lactation

Mothers with diabetes using insulin may nurse their infants. Exogenous insulin is excreted into breastmilk, including newer biosynthetic insulins (e.g., aspart, degludec, detemir, glargine glulisine, lispro). Even direct administration of recombinant insulin orally to preterm infants is safe.[1] Insulin is a normal component of breastmilk and may decrease the risk of type 1 diabetes in breastfed infants.[2-5] Women taking insulin for type 2 diabetes have higher milk insulin levels than those controlled with diet alone.[6]

Insulin requirements are reduced postpartum in women with type 1 diabetes,[7,8] although postpartum insulin requirements do not significantly differ between breastfeeding and non-breastfeeding women.[9] In general, insulin requirements are 30% to 50% lower than prepregnancy dosages immediately postpartum. Then the

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insulin requirements during breastfeeding average 21% lower than prepregnancy dosages, but there is wide variation.[8,10] In one study, insulin requirements were lower than prepregnancy dosage only during the first week postpartum: 54% of prepregnancy dosage on day 2 and 73% on day 3 postpartum. On day 7 postpartum, insulin dosage returned to prepregnancy requirements.[11] Another study found that dosage requirements did not return to normal for up to 6 weeks in some mothers.[12] A third study found that at 4 months postpartum, patients with type 1 diabetes who exclusively breastfed had an average of 13% lower (range -52% to +40%) insulin requirement than their prepregnancy requirement.[13] A retrospective case-control study found a 34% decrease in postpartum insulin requirement compare to preconception values. There was a nonsignificant trend towards lower requirements in exclusively breastfeeding mothers compared to partial or full formula feeding.[6] A small study found that mothers on insulin pumps were found to have an average basal insulin rates 14% lower and carbohydrate-to-insulin ratios were 10% higher than pre-pregnancy settings.[14] Breastfeeding appears to improve glucose postpartum glucose tolerance in mothers with gestational diabetes mellitus and in normal women.[15-17]

A small, well-controlled study of women with type 1 diabetes mellitus using continuous subcutaneous insulin found that the average basal insulin requirement in women with type 1 diabetes who breastfed was 0.21 units/kg daily and the total insulin requirement was 0.56 units/kg daily. In similar women who did not breastfeed, the basal insulin requirement was 0.33 units/kg daily and the total insulin requirement was 0.75 units/kg daily. The 36% lower basal insulin requirement was thought to be caused by glucose use for milk production.[18]

Lactation onset occurs later in patients with type 1 diabetes than in women without diabetes, with a greater delay in mothers with poor glucose control.[11,19] Mothers with type 1 diabetes also discontinue nursing at a higher rate during the first week postpartum.[20-22] Women with any form of diabetes during pregnancy had more problems with low milk supply than women without diabetes.[23] Once established, lactation persists as long in mothers with diabetes as in mothers without diabetes.[19,24] However, as in women without diabetes, smoking has a strong negative impact on lactation among mothers with type 1 diabetes.[13,25] Other factors that have been identified as causes of shorter duration of breastfeeding among type 1 diabetic patients are more frequent caesarean sections and earlier delivery.[26] Among patients with gestational diabetes, those treated with insulin have a delayed onset of lactogenesis II compared to those not treated with insulin.[27]

Drug Levels

Maternal Levels. Insulin is normally present in breastmilk.[28,29] In one study, insulin levels in milk were 60 milliunits/L (range 6.5 to 306 milliunits/L) in 42 mothers without diabetes who had fullterm infants between 3 and 30 days postpartum.[2] Insulin levels averaged 59 milliunits/L on day 3 postpartum and 40 milliunits/L on day 7 postpartum in 24 mothers without diabetes who had fullterm infants. Mothers of preterm infants had nonsignificant changes in milk insulin levels.[30]

In a study of 7 diabetic nursing mothers and 10 nondiabetic nursing mothers, blood glucose was elevated to about 300 mg/dL using a continuous intravenous glucose infusion. Regular pork insulin was then given intravenously to lower the blood glucose. Glucose and insulin were measured in the breastmilk of all the mothers. The milk glucose of women with diabetes approximately tripled during the experiment, but milk glucose remained low in the nondiabetic women. Milk insulin was elevated in the diabetic women, with the peak milk insulin level occurring between 30 to 50 minutes after the intravenous injection. Nine of the 10 nondiabetic women had detectable insulin levels in breastmilk which ranged from 5.1 to 13 milli-IU/mL.[31]

Insulin was measured in donor milk from 34 nondiabetic women who were between 1 month and 1 year postpartum. The average insulin concentration was 163 picomoles/L. After pasteurization using the Holder method (62.5 degrees C for 30 min), the average concentration was 88 picomoles/L.[32]

A small study measured breastmilk insulin concentrations in control mothers (n = 5; 1 to 6 months postpartum), mothers with type 1 diabetes mellitus (n = 4; 2 to 5 months postpartum) and type 2 diabetes (n = 5; 5 to 6 months postpartum). No differences were found in the insulin content among the 3 groups and little circadian variation was found. Mothers with type 1 diabetes were well controlled on insulin aspart and insulin glargine. No endogenous insulin was found in their breastmilk, but the milk of 3 of the mothers contained an average 20.5 milliunits/L of insulin, presumed to be of exogenous origin. No indication of paracellular diffusion of insulin was apparent in these women and C-peptide levels in milk were only 5 to 7% those of control mothers. These findings indicate that insulin is likely actively transported into breastmilk.[33]

A cohort study compared insulin levels in the breastmilk of mothers who had normal weight and those who were overweight or obese. Breastmilk insulin concentrations were higher in the overweight and obese mothers at 2 weeks, 1 month and 3 months postpartum. The average milk insulin concentration was almost twice as great as fasting insulin serum insulin in one study at 2 weeks postpartum and a third higher at 4 months postpartum.[34]

A study compared milk insulin levels in mothers who either had type 2 diabetes controlled with insulin with or without oral agents, women whose glucose was controlled by diet alone or women without diabetes. The group receiving insulin had higher milk insulin levels than the other two groups and their milk insulin increased as mean nocturnal serum glucose increased.[6]

A study of the milk of the mothers of preterm infants found insulin levels to average 86.4 pmol/L in the first 2 months postpartum and 119.1 pmol/L in months 3 to 6 postpartum, which was a statistically significant difference. The average concentration of insulin in preterm milk was 109.1 pmol/L over the first 6 months postpartum compared to 96.7 pmol/L in the milk of fullterm milk, although this difference was not statistically significant.[35]

Infant Levels. Relevant published information was not found as of the revision date.

Effects in Breastfed Infants

Relevant published information was not found as of the revision date. Insulin in breastmilk is thought to be necessary for intestinal maturation of the infant and may help decrease the risk of contracting type 1 diabetes in breastfed infants.[2,3]

Effects on Lactation and Breastmilk

Proper insulin levels are necessary for lactation. Good glycemic control enhances maternal serum and milk prolactin concentrations and decreases the delay in the establishment of lactation that can occur in mothers with type 1 diabetes.[19,36]

One-hundred two of 107 consecutive mothers with type 1 diabetes mellitus who delivered were followed at a Danish hospital. Mothers were given prenatal information on breastfeeding and were offered postnatal counseling by a nurse on the benefits of breastfeeding. All infants were admitted to the neonatal intensive care unit at about 2 hours of age for the following 24 hours. When possible, mothers either breastfed or pumped milk for their infants during this time. Mothers were contacted at 5 days and 4 months postpartum to determine their breastfeeding status. The rates of initiation of exclusive and nonexclusive breastfeeding and exclusive formula feeding and the rates at 4 months postpartum were no different from those of the Danish population.[13]

Eight hundred eighty-three women with gestational diabetes were interviewed at 6 to 9 weeks postpartum. Those who had been treated with insulin more frequently reported having a delayed onset of lactogenesis II (>72 hours) postpartum than those not treated with insulin, independent of other maternal risk factors. The odds ratio of having delayed lactogenesis II was 3.1 among insulin-treated mothers compared to mothers with gestational diabetes who did not receive insulin.[27]

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Substance Identification

Substance Name

Insulin

CAS Registry Number

11061-68-0

Drug Class

Breast Feeding

Lactation

Milk, Human

Hypoglycemic Agents