REVIEW

Возможности применения инсулина детемир при лечении сахарного диабета у беременных: доказанные преимущества и перспективы использования

© Руяткина Л.А.[1], Сорокин М.Ю.[2]

[1]ГБОУ ВПО Новосибирский государственный медицинский университет, Новосибирск
[2]ГБУЗ Новосибирской области Городская клиническая больница №1, Новосибирск

В последние годы наблюдается рост распространенности гестационного и манифестного сахарного диабета (СД) у беременных женщин при сохраняющемся высоком уровне акушерских осложнений, неонатальной заболеваемости, перинатальной смертности у женщин с различными формами СД в сравнении с популяцией. Также не вызывает сомнения комплексный вклад фетального программирования и генетических факторов в формирование различных патологических состояний в будущем у детей, рожденных от матерей, страдающих СД.
Доказано снижение риска возникновения акушерских осложнений при достижении удовлетворительного контроля гликемии. Улучшенный фармакокинетический и фармакодинамический профиль аналогов инсулина (в том числе минимальная вариабельность действия) позволяют достигать лучшего контроля гликемии при более низком риске гипогликемий в сравнении с человеческими инсулинами. Клинические преимущества детемира были подтверждены в исследованиях у беременных пациенток с СД. Детемир – единственный аналог инсулина длительного действия, изучавшийся в проспективных исследованиях у беременных женщин – доказал свой удовлетворительный профиль безопасности, а также возможность достижения более низкого уровня гликемии натощак и большей зрелости плода на момент родов.
Ключевые слова: *сахарный диабет; беременность; инсулинотерапия; детемир; вариабельность гликемии; фетальное программирование*

Detemir potential applications in the treatment of diabetes during pregnancy: proven benefits and perspectives

L.A. Ruyatkina[1], M.Y. Sorokin[2]

[1]Novosibirsk State Medical University, Novosibirsk, Russia
[2]Novosibirsk City Clinical Hospital #1, Novosibirsk, Russia

In recent years there is notable growing prevalence of gestational and overt diabetes in pregnant women while rate of obstetric complications, neonatal morbidity, perinatal mortality in women with diabetes is maintained at the high level as compared with common population. Furhermore no doubt that fetal programming and genetic factors induce the formation of various longterm complications in infants of diabetic mothers.
There is a strong evidence that the risk of obstetric complications can be reduced by achieving adequate glycemic control, which is frequently still an elusive goal. Improved pharmacokinetic and pharmacodynamic profiles of the insulin analogs (including minimal action variability) allow to achieve a better glycemic control with lower risk of hypoglycemias compared to human insulin. The clinical benefits of detemir have been confirmed in clinical trials in pregnant women with diabetes. Detemir is the only long-acting insulin analog that has been evaluated in prospective studies in pregnant women and proved a satisfactory safety profile and the ability to achieve a lower level of fasting glycemia and advanced maturity of the fetus at delivery.
Keywords: *diabetes mellitus; pregnancy; insulin therapy; detemir; glycemic variability; fetal programming*

As shown at the 7th International DIP Symposium on Diabetes, Hypertension, Metabolic Syndrome and Pregnancy conducted in Florence from 13 to 16 March, 2013, the prevalence of diabetes mellitus (DM) in pregnant women is increasing, and the rates of neonatal morbidity and perinatal mortality are higher in women with different forms of DM compared with those in the general population. Experts stated that the Saint Vincent Declaration targets of 1989 [1] to achieve successful carrying of pregnancies in women with DM similar to that in healthy women have not yet been accomplished. To date, reports regarding insulin therapy have noted that there is little evidence concerning the benefits of using insulin analogues during pregnancy; however, their appropriate

Received: 21.07.2015. Accepted: 15.10.2015.
Сахарный диабет. 2016;19(2):171-178 DOI: 10.14341/DM2004150-55 Diabetes Mellitus. 2016;19(2):171-178

application can play a significant role in achieving the goals of the Saint Vincent Declaration [2]. These circumstances highlight the importance of discussing the potential application of modern insulins in the treatment of gestational diabetes mellitus (GDM).

Insulin therapy is the basic treatment for type 1 diabetes (T1D), GDM and type-2 diabetes (T2D) during pregnancy when the compensation of carbohydrate metabolism and prevention of complications cannot be solely achieved by diet interventions and physical activity modifications. Human insulin preparations have been widely used during pregnancy, and have been demonstrated to improve the neonatal and maternal pregnancy outcomes in pregnant women with DM [3].

The proven benefits of insulin analogues in improving fasting glycemia (using basal insulin analogues), postprandial glycemia (using ultra-short-acting insulin analogues) and HbA1c combined with the lower risk of hypoglycemia compared with human insulins [4], make them a superior choice in treating DM in pregnant women. As a result of thorough evaluations of the efficacy and safety of insulin analogues, some of them have been approved for use during pregnancy, including aspart (NovoRapid), detemir (Levemir) [according to the US Food and Drug Administration (FDA), both are classified in the pregnancy risk category B], lispro (Humalog) (pregnancy risk category B) and glargine (Lantus) (pregnancy risk category C).

Hyperglycemia and pregnancy outcomes

Monitoring carbohydrate metabolism during pregnancy is associated with a reduced risk of maternal, fetal and neonatal complications [5]. The distinctive features of glycemic control during pregnancy include excellent glycemic control as early as in the first trimester, with HbA1c levels maintained during pregnancy as close to normal values as possible with minimal risk of hypoglycemia.

Hyperglycemia in the first trimester is the main risk factor for miscarriage [6-8] and fetal malformations; the incidence of these outcomes in a group of pregnant women with T1D was found to be 2–10 times higher compared with that in the general population [9-11]. The risks of these events depend on the severity of hyperglycaemia [12, 13] and significantly increase at HbA1c levels being higher than three standard deviations greater than the HbA1c levels of healthy women (>6.3%) [14-18].

After the 12th week of gestation, hyperglycemia leads to hyperinsulinemia of the fetus, fetal growth acceleration and an increase in the amount of adipose tissue. Macrosomia (neonate birth weight of >4000–4500 g) occurs in 27%–62% of pregnant women with DM and is 3–6 times more common in women with DM than in women without DM; the incidence of macrosomia in the latter group is approximately 10% [19]. In turn, macrosomia is associated with increased incidences of operative delivery and obstetric trauma, antenatal fetal death and neonatal complications, including hypoglycemia, hypertrophic cardiomyopathy, polycythemia and hyperbilirubinemia [14]. Long-term follow-up of infants born to mothers with decompensated carbohydrate metabolism during pregnancy has demonstrated a more frequent development of intellectual and psychomotor disorders in these children [14]. Macrosomia and fetal hyperinsulinemia increase the risk of obesity and carbohydrate metabolism disorders during subsequent life [14, 20].

It is a challenging task to achieve the target values of glycemia during pregnancy. Only 40%–60% of pre-GDM women manage to achieve stable euglycemia that is attributed to the presence of additional factors preventing the corresponding release of insulin relative to the glucose level during pregnancy. These factors include constantly changing insulin requirements; decreased insulin sensitivity resulting from physiological hypercortisolism; physiological hyperprolactinemia; adipose tissue mass gain; increased placental insulinase activity (which in turn contributes to a significant reduction in the elimination half-life of insulin preparations as well as a need to increase the frequency of basal insulin injections); a lack of hypoglycemia awareness; toxicosis phenomena that contribute to the unbalanced administration of short/ultra-short-acting insulin doses and carbohydrate intake [21].

Diabetes mellitus and foetal programming

A population-based cohort study of 1,781,576 singletons born in Denmark was aimed at follow-up of the infants up to 30 years [22]. An increased risk of malignant neoplasm was found in children prenatally exposed to maternal T2D [hazard ratio (HR): 2.2, 95% confidence interval (CI): 1.5–3.2]. An increased risk of circulatory system diseases was found in children exposed to maternal T1D (HR: 2.2, 95% CI: 1.6–3.0), T2D (HR: 1.4, 95% CI: 1.1–1.7) and GDM (HR: 1.3, 95% CI: 1.1–1.6).

Data from large-scale studies have provided evidence that high birth weight, which is often related to maternal DM, is associated with increased risk of cancer, including breast cancer [23], prostate cancer [24], colorectal cancer [25], endometrial cancer [26], astrocytomas [27-29] and acute childhood lymphoblastic and myeloid leukemias [30].

At an early age, infants of mothers with DM have higher insulin resistance and higher cardiometabolic risks [31, 32]. The results of long-term trials have showed a positive correlation between glucose control during pregnancy in mothers with T1D and fasting glucose, BMI and systolic blood pressure in the young adults [33]. Thus, it can be supposed that the mother's hyperglycemia has a special prenatal imprinting on their children; that is, fetal programming and genetic factors may contribute to adverse health issues later in life in infants of mothers with DM. In this situation, it is important to take into account any details that may facilitate adequate control of DM during pregnancy.

Glycemic variability, hypoglycemic risk and pregnancy outcomes

In the first trimester of pregnancy, glucose is actively absorbed by the developing placenta and peripheral tissues, and the levels of gluconeogenesis substrates (primarily amino acids) and, therefore, hepatic glucose production decrease, leading to a decrease in glycemia, particularly in the morning. Therefore, these factors are associated with a 10–20% decline in insulin requirement in the first trimester [34]. As a result, the frequency of severe hypoglycemia and hypoglycemic coma during the first trimester of T1D pregnancy may rise almost three and more than two times versus before gestation, respectively [35].

Severe hypoglycemia in the first trimester is associated with a history of severe hypoglycemia before gestation, 10 years' longer DM duration, HbA1c levels of <6.5% and a 0.1 unit/kg higher daily insulin dose [35]. First trimester hypoglycemia may also result from early gestational toxicosis and the forced refusal of adequate carbohydrate intake.

Therefore, the pharmacokinetic characteristics of basal insulins must be taken into account. For example, administration of Neutral Protamine Hagedorn (NPH) insulin at bedtime often causes nocturnal hypoglycemia due to the pharmacokinetic profile of this insulin, with peak action at 3–4 h at night. In addition, variability of the pharmacokinetic and pharmacodynamic profiles of insulin preparations is one of the main obstacles to achieving optimal glycemic control [36, 37]. The absorption variability of NPH insulin from the injection site varies from 10% to 52%, which explains the unpredictability of its action and the increased risk of hypoglycemia in pregnant women [38].

Insulin detemir (Levemir) is characterised by protracted and flat absorption that results from increased self-assembly into hexamers in the subcutaneous tissue and reversible albumin binding via a myristic fatty acid residue attached to the amino acid lysine B29 [39]. Insulin detemir shows a slower onset of action, with no pronounced peak, and a longer duration of action compared with NPH insulin [40, 41].

Pharmacodynamic studies have shown that in T1D and T2D, insulin detemir has significantly lower variability of action [41-43] and, therefore, a more predictable glucose-lowering effect than other basal insulins (Fig. 1). Lower variability of insulin detemir has also been demonstrated in several clinical studies of patients with DM [44, 45].

The low variability of detemir absorption is associated with reduced risk of hypoglycemia compared with NPH insulin [46]. Clinical trials in patients with T1D and T2D have shown reduced total rates of hypoglycaemia and nocturnal hypoglycemia in those using detemir compared with those using NPH insulin [47-49]. Of great practical interest is the data from a study conducted in healthy volunteers showing that administration of detemir leads to increased symptom response and awareness during hypoglycemia compared with human insulin [50].

In addition, glycemic variability was found to be correlated with diabetic autonomic imbalance [51] and oxidative stress [52] in patients with T1D and T2D. Previously, oxidative stress was shown to be a leading factor of the pathogenesis of fetal malformations caused by hyperglycemia [53, 54]; further, it increases the rates of spontaneous abortions, recurrent miscarriage, pre-eclampsia and intrauterine growth restriction [55]. Oxidative stress induced by glycemic variability may be associated with the microvascular and macrovascular complications of DM [56, 57].

It should also be considered that therapy with insulin analogues improves quality of life, treatment success, satisfaction and adherence [58], which are of particular importance in the treatment of DM in pregnant women. Experts from the International Diabetes Federation have noted that, given the limited experience in the use of insulin analogues, the decision on the choice of insulin medication during pregnancy should be agreed on with the patient, taking into account the possibility of achieving better compensation of carbohydrate metabolism during treatment with the drug [59].

Influence of detemir on body weight

Body weight control when planning pregnancy and prenatal care in patients with DM is particularly important. Maternal obesity increases the risk of congenital anomalies [60, 61] and is also associated with higher risks of adverse pregnancy outcomes, including arterial hypertension and pre-eclampsia, GDM, the need for delivery induction, caesarean section, stillbirth, perinatal mortality, macrosomia, premature birth, obesity in the childhood and T2D occurrence in the offspring [61, 62].

Up to one-third of pregnant women experience excessive weight gain during pregnancy [63]. Weight gain of more than 16 kg during pregnancy in women with GDM

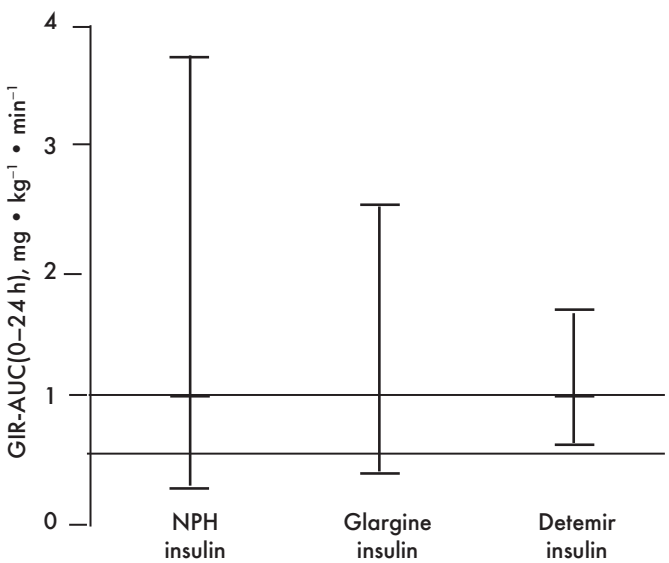

Fig. 1. Differences in the pharmacokinetic variability coefficients of NPH, glargine and detemir insulins [43].
Note: GIR-AUC = glucose infusion rate-area under the curve.

receiving insulin therapy may increase the risk of large for gestational age infants by six times [64]. Maternal weight gain in the first trimester can be used to predict newborn size more accurately than weight gain in the third trimester. Specifically, a 1 kg maternal weight gain in the first trimester corresponds to a 31 g mean increase in newborn weight ($p < 0.0007$) and a 1 kg maternal weight gain in the second trimester corresponds to a 26 g mean increase in newborn weight ($p < 0.007$); however, maternal weight gain in the third trimester is not associated with an increase in newborn weight [65]. In general, the combination of DM and obesity during pregnancy significantly contributes to foetal programming and also has a negative consequence on subsequent generations (Fig. 2).

Despite the negative impact of obesity on the course and outcome of pregnancy, it is not recommended for pregnant women to diet to reduce their body weight. However, in pregnant women with GDM who are overweight, dietary energy restriction to 30% of their usual dietary consumption [66] does not lead to ketosis and does not have any negative effects [67]. According to the Cochrane Central Register of Controlled Trials, dietary interventions prevented excessive gestational weight gain (mean of 1.92 kg, $p = 0.03$) and reduced the need for caesarean section (relative risk: 0.75, 95% CI: 0.60–0.94, $p = 0.013$). However, dietary intervention had no significant effect on birth weight, pre-eclampsia, GDM or preterm birth [68].

Traditionally, improvements in glycemic control during insulin therapy are associated with weight gain [69]. Insulin detemir showed no negative influence on weight gain over time in T1D [48, 70] and a lower tendency of weight gain in patients with T2D [49, 71], thus offering additional benefits in terms of outcomes in the treatment of DM during pregnancy.

This effect of insulin detemir (Levemir) on body weight may result from its effect on the brain, as well as the ability of the central nervous system to help regulate

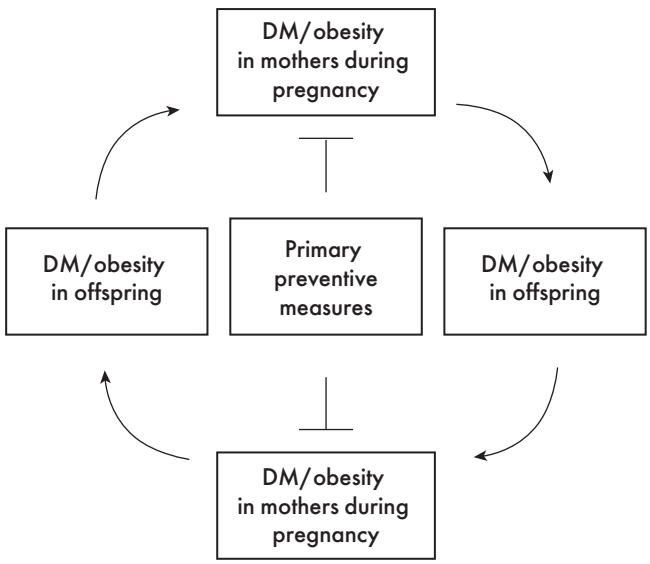

Fig. 2. Primary preventive measures of DM/obesity (adapted from P.G. Ovesen, D.M. Jensen [eds.], Maternal Obesity and Pregnancy, Springer-Verlag Berlin Heidelberg, 2012).

hunger and satiety, hypoglycemia risk reduction, greater hepatoselectivity, lower lipotropism and the ability to alleviate deficient incretin function via the increased secretion of GLP-1 [72-75]. The data obtained in the analysis of non-pregnant patients with DM suggest new additional opportunities in the treatment of patients experiencing difficulties in controlling weight gain during pregnancy.

Peculiarities of insulin therapy for gestational diabetes

The prevalence of GDM continues to grow worldwide. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study, one of the largest studies in obstetrics practice [76], found that the risks of adverse pregnancy outcomes rise even at maternal glucose levels below those diagnostic of DM. Based on the results of the HAPO study, the experts of the International Association of the Diabetes and Pregnancy Study Groups, as well as those of the Russian Association of Endocrinologists and the Russian Society of Obstetricians and Gynaecologists, began glycemic targets of self-control [77, 78]. According to these recommendations, in order to minimise the risk of adverse pregnancy outcomes, one should strive to maintain fasting glycemia from 3.3 to 5.1 mmol/L before meals and 7.0 mmol/L 1 h after meals.

GDM is characterised by insulin resistance, which is the major contributor to the pathogenesis of hyperglycemia; high doses of insulin are required to manage insulin resistance in some cases, which is accompanied by higher risk of hypoglycemia.

When prandial correction of glycemia in pregnant woman with GDM is required, a basal-bolus regimen of insulin therapy demonstrated benefits versus premixed insulin preparations and short-acting insulin both in terms of improved glycemic control and pregnancy outcomes [79].

During insulin therapy for GDM, achievement of stable glycemia using insulin medications with narrow therapeutic windows requires the selection of a drug with stable pharmacokinetic and pharmacodynamic profiles, with weakly pronounced peak action, minimal risk of hypoglycaemia and no negative impact on body weight.

Use of detemir during pregnancy: evidence-based medicine perspective

The first publications of retrospective analysis data of cases of detemir treatment during pregnancy appeared in 2009–2010. Satisfactory maternal and foetal safety profiles of detemir were demonstrated in a study of 11 women with T1D [80, 81]. Detemir was shown to have a lower IGF-1 receptor affinity and, therefore, lower mitogenic potential compared with human insulin [82]. This suggested its safety in terms of teratogenesis, which was confirmed by the data of a recently published clinical trial involving 470 women with T1D [83].

In contrast to glargine, the effects of detemir (Levemir) were studied in pregnant women with T1D in a planned prospective randomised trial that compared the efficacy and safety of insulin detemir with NPH (both in combination with insulin aspart) (n = 310) [84]. Randomisation was performed within 12 months prior to conception (48%) or at 8–12 weeks of pregnancy (52%).

The results showed that in the treatment of T1D in pregnant women, insulin detemir was not inferior to NPH in terms of the degree of achieved carbohydrate metabolism compensation. The HbA1c levels at the 36th week of pregnancy (primary endpoint) in the groups treated with detemir and NPH did not differ significantly (6.27% and 6.33%, respectively). Additionally, the levels of fasting glucose were significantly lower in the detemir group both at the 24th week (5.4 versus 6.3 mmol/L, p = 0.012) and at the 36th week of gestation (4.8 versus 5.4 mmol/L, p = 0.017) at comparable rates of mild and severe hypoglycemia.

Subsequent analysis of the effect of therapy with detemir and NPH on pregnancy outcomes showed no significant differences in the incidences of maternal and fetal adverse pregnancy outcomes (including malformations) [83]. Congenital malformations were detected in eight newborns in each group (5.6%, n = 8/142 when using detemir and 5.5%, n = 8/145 when using NPH). Further, the incidence of other adverse events did not differ significantly between the treatment groups.

The detemir and NPH groups included 128 and 136 live-born infants, 11 and 9 early spontaneous abortions and 1 and 2 cases of perinatal deaths, respectively. There were no significant differences in the pregnancy outcomes, the frequency of spontaneous abortions, the incidence of pre-eclampsia, malformations, foetal macrosomia, preterm delivery, stillbirth, perinatal mortality, or neonatal hypoglycemia. The newborns were delivered at a significantly older gestational age in the detemir group compared with that in the NPH group: 38.2 versus 37.8 weeks, respectively (difference of 0.49 weeks, 95% CI: 0.11–0.88, p = 0.012). Similar results in terms of delivery at an older gestational age were obtained in a study comparing T1D therapy during pregnancy with another insulin analogue, aspart, with short-acting human insulin [85], which implies advanced maturity of the fetus at delivery.

A study by Mathiesen et al convincingly demonstrated that treatment with detemir initiated during the planning of pregnancy allows to achieve lower levels of fasting glucose and HbA1c without increasing the risk of hypoglycaemia [84]. These figures are extremely important for reducing the risk of adverse pregnancy outcomes.

Conclusions

The results of the world-famous HAPO study [76] indicated strong, continuous associations of maternal hyperglycemia less severe than that in DM with risks of adverse pregnancy outcomes. Additionally, there is no doubt regarding the association between the degree of carbohydrate metabolism disorders in pregestational DM with the risks of malformations, miscarriage and foetal macrosomia [7, 18, 86].

Meanwhile, achieving near normal glycemic values during pregnancy is an extremely challenging, and often elusive task, particularly in T1D. In particular, it is difficult to imitate the physiological profile of basal and prandial insulin secretion needed to maintain stable glycemic values, and the problem of hypoglycemia has not yet been resolved. There is limited evidence to establish a ‘gold standard’ in insulin therapy of pregestational DM during pregnancy.

The benefits of insulin detemir (Levemir) considered in this review may be important when choosing a basal insulin for DM treatment during pregnancy in clinical practice. Improved pharmacokinetic and pharmacodynamic profiles of detemir (including minimal action variability), in addition to the results of clinical trials on non-pregnant patients with T1D and T2D, indicate improved glycemic control with a lower risk of hypoglycemia and neutral effects on body weight. The clinical benefits of detemir have been confirmed in pregnant women with DM. These data formed the basis for the reconsideration and change of the pregnancy risk category of insulin detemir from C to B (according to the FDA), as well as the changes to the information on the medical use of insulin detemir, with expansion of the indications for use of detemir in pregnant women (instructions on the application of Levemir® FleksPen® medication for specialists are available at: http://www.vidal.ru/poisk_preparatov/levemir-flexpen.htm).

All of the above add to a powerful argument in favour of the use of detemir during both the pregnancy-planning stage to achieve the targets of glycemic control and near normal levels of HbA1c and during pregnancy, which could lead to the decreased risk of congenital malformations and miscarriage.

Financing and conflicts of interest

No external financial support was provided for the writing and publishing of this article.

The authors declare no obvious or any other conflicts of interest related to the publication of this paper.

References

1. Diabetes Care and Research in Europe: The Saint Vincent Declaration. *Diabetic Medicine*. 1990;7(4):360-360. doi: 10.1111/j.1464-5491.1990.tb01405.x
2. Тиселько А.В. Международный симпозиум «Диабет, Гипертония, Метаболический синдром и Беременность», 13–16 марта 2013 г., Флоренция, Италия. // Сахарный диабет. – 2013. – Т. 16. – №1 – С.106-107. [Tiselko AV. The 7th International DIP Symposium on Diabetes, Hypertension, Metabolic Syndrome and Pregnancy March 13th–16th, 2013, Florence, Italy. *Diabetes mellitus*. 2013;16(1):106-107. (In Russ).] doi: 10.14341/2072-0351-3605
3. Jovanovic-Peterson L, Kitzmiller JL, Peterson CM. Randomized trial of human versus animal species insulin in diabetic pregnant women: improved glycemic control, not fewer antibodies to insulin, influences birth weight. *Am J Obstet Gynecol*. 1992;167:1325-1330. doi: 10.1016/S0002-9378(11)91710-4
4. Rossetti P, Porcellati F, Fanelli CG, et al. Superiority of insulin analogues versus human insulin in the treatment of diabetes mellitus. *Archives of physiology and biochemistry*. 2008;114(1):3-10. doi: 10.1080/13813450801900777
5. Kitzmiller JL, Block JM, Brown FM, et al. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. *Diabetes care*. 2008;31(5):1060-1079. doi: 10.2337/dc08-9020
6. Key TC, Giuffrida R, Moore TR. Predictive value of early pregnancy glycohemoglobin in the insulin-treated diabetic patient. *American Journal of Obstetrics & Gynecology*. 1987;156(5):1096-1100. doi: 10.1016/0002-9378(87)90117-7
7. Mills JL, Simpson JL, Driscoll SG, et al. Incidence of Spontaneous Abortion among Normal Women and Insulin-Dependent Diabetic Women Whose Pregnancies Were Identified within 21 Days of Conception. *New England Journal of Medicine*. 1988;319(25):1617-1623. doi: 10.1056/NEJM198812223192501
8. Rosenn B, Miodovnik M, Combs CA, et al. Preconception management of insulin-dependent diabetes: improvement of pregnancy outcome. Obstet Gynecol. 1991;77:846-9.
9. Casson IF, Clarke CA, Howard CV, et al. Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. *BMJ*. 1997;315(7103):275-278. doi: 10.1136/bmj.315.7103.275
10. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ*. 2004;328(7445):915. doi: 10.1136/bmj.38043.583160.EE.
11. Macintosh MC, Fleming KM, Bailey JA, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. *BMJ*. 2006;333(7560):177. doi: 10.1136/bmj.38856.692986.AE
12. Kitzmiller JL, Buchanan TA, Kjos S, et al. Pre-conception care of diabetes, congenital malformations, and spontaneous abortions (ADA Technical Review). *Diabetes Care*. 1996;19:514–41. doi: 10.2337/diacare.19.5.514
13. 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. *QJM*. 2001;94(8):435-444. doi: 10.1093/qjmed/94.8.435
14. Kitzmiller JL, Block JM, Brown FM, et al. Managing Preexisting Diabetes for Pregnancy: Summary of evidence and consensus recommendations for care. *Diabetes care*. 2008;31(5):1060-1079. doi: 10.2337/dc08-9020
15. Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with Type I diabetes mellitus. *Diabetologia*. 2000;43(1):79-82. doi: 10.1007/s001250050010
16. Temple R, Aldridge V, Greenwood R, et al. Association between outcome of pregnancy and glycaemic control in early pregnancy in type 1 diabetes: population based study. *BMJ*. 2002;325(7375):1275-1276. doi: 10.1136/bmj.325.7375.1275
17. Kerssen A, Evers IM, de Valk HW, Visser GHA. Poor glucose control in women with type 1 diabetes mellitus and 'safe' hemoglobin A1c values in the first trimester of pregnancy. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2003;13(5):309-313. doi: 10.1080/jmf.13.5.309.313
18. Nielsen GL, Møller M, Sørensen HT. HbA1c in Early Diabetic Pregnancy and Pregnancy Outcomes: A Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. *Diabetes care*. 2006;29(12):2612-2616. doi: 10.2337/dc06-0914
19. Gabbe SG, Graves CR. Management of diabetes mellitus complicating pregnancy. *Obstetrics and gynecology*. 2003;102(4):857-868. doi: 10.1016/j.obstetgynecol.2003.07.001
20. Fetita LS, Sobngwi E, Serradas P, et al. Consequences of fetal exposure to maternal diabetes in offspring. *The Journal of clinical endocrinology and metabolism*. 2006;91(10):3718-3724. doi: 10.1210/jc.2006-0624
21. Kauffman RP. The Diabetes in Pregnancy Dilemma: Leading Change with Proven Solutions. *J Am Med Assoc*. 2006;296:1530-1531.
22. Wu CS, Nohr EA, Bech BH, et al. Long-term health outcomes in children born to mothers with diabetes: a population-based cohort study. *PloS one*. 2012;7(5):e36727. doi: 10.1371/journal.pone.0036727
23. Mellemkjær L, Olsen M, Sørensen H, et al. Birth weight and risk of early-onset breast cancer (Denmark). *Cancer Causes Control*. 2003;14(1):61-64. doi: 10.1023/A:1022570305704
24. Nilsen TI, Romundstad PR, Troisi R, Vatten LJ. Birth size and subsequent risk for prostate cancer: a prospective population-based study in Norway. *International journal of cancer*. 2005;113(6):1002-1004. doi: 10.1002/ijc.20674
25. Nilsen TI, Romundstad PR, Troisi R, et al. Birth size and colorectal cancer risk: a prospective population based study. *Gut*. 2005;54(12):1728-1732. doi: 10.1136/gut.2004.060475
26. McCormack VA, dos Santos Silva I, Koupil I, et al. Birth characteristics and adult cancer incidence: Swedish cohort of over 11,000 men and women. *International journal of cancer*. 2005;115(4):611-617. doi: 10.1002/ijc.20915
27. Heuch JM, Heuch I, Akslen LA, Kvale G. Risk of primary childhood brain tumors related to birth characteristics: a Norwegian prospective study. *International journal of cancer*. 1998;77(4):498-503. doi: 10.1002/(SICI)1097-0215(19980812)77:4<498::AID-IJC4>3.0.CO;2-P
28. Von Behren J, Reynolds P. Birth characteristics and brain cancers in young children. *International journal of epidemiology*. 2003;32(2):248-256. doi: 10.1093/ije/dyg057
29. Mogren I, Malmer B, Tavelin B, Damber L. Reproductive Factors Have Low Impact on the Risk of Different Primary Brain Tumours in Offspring. *Neuroepidemiology*. 2003;22(4):249-254. doi: 10.1159/000070567
30. Hjalgrim LL, Westergaard T, Rostgaard K, et al. Birth Weight as a Risk Factor for Childhood Leukemia: A Meta-Analysis of 18 Epidemiologic Studies. *American Journal of Epidemiology*. 2003;158(8):724-735. doi: 10.1093/aje/kwg210
31. Krishnaveni GV, Veena SR, Hill JC, et al. Intrauterine Exposure to Maternal Diabetes Is Associated With Higher Adiposity and Insulin Resistance and Clustering of Cardiovascular Risk Markers in Indian Children. *Diabetes care*. 2010;33(2):402-404. doi: 10.2337/dc09-1393
32. Tam WH, Ma RCW, Yang X, et al. Glucose Intolerance and Cardiometabolic Risk in Adolescents Exposed to Maternal Gestational Diabetes: A 15-year follow-up study. *Diabetes care*. 2010;33(6):1382-1384. doi: 10.2337/dc09-2343
33. Khoury JC, Dolan LM, VanDyke R, et al. Fetal development in women with diabetes: imprinting for a life-time? *The Journal of Maternal-Fetal & Neonatal Medicine*. 2012;25(1):11-14. doi: 10.3109/14767058.2012.626921
34. Jovanovic L, Knopp RH, Brown Z, et al. Declining Insulin Requirement in the Late First Trimester of Diabetic Pregnancy. *Diabetes care*. 2001;24(7):1130-1136. doi: 10.2337/diacare.24.7.1130
35. Evers IM, ter Braak EWMT, de Valk HW, et al. Risk Indicators Predictive for Severe Hypoglycemia During the First Trimester of Type 1 Diabetic Pregnancy. *Diabetes care*. 2002;25(3):554-559. doi: 10.2337/diacare.25.3.554
36. Scholtz HE, van Niekerk M, Meyer BH, et al. An assessment of the variability in the pharmacodynamics (glucose lowering effect) of HOE901 compared to NPH and ultralente human insulins using the euglycaemic clamp technique (Abstract). *Diabetologia*. 1999;42(1):235.
37. Ziel FH, Davidson MB, Harris MD, Rosenberg CS. The Variability in the Action of Unmodified Insulin is More Dependent on Changes in Tissue Insulin Sensitivity than on Insulin Absorption. *Diabetic Medicine*. 1988;5(7):662-666. doi: 10.1111/j.1464-5491.1988.tb01076.x
38. Jovanovic L, Pettitt DJ. Treatment with insulin and its analogs in pregnancies complicated by diabetes. *Diabetes care*. 2007;30 Suppl 2:S220-224. doi: 10.2337/dc07-s220
39. Kurtzhals P. Engineering predictability and protraction in a basal insulin analogue: the pharmacology of insulin detemir. *International journal of obesity and related metabolic disorders*. 2004;28 Suppl 2:S23-28. doi: 10.1038/sj.ijo.0802746
40. Heinemann L, Sinha K, Weyer C, et al. Time-action profile of the soluble, fatty acid acylated, long-acting insulin analogue NN304. *Diabetic medicine*. 1999;16(4):332-338. doi: 10.1046/j.1464-5491.1999.00081.x
41. Pieber TR, Plank J, Goerzer E, et al. Duration of action, pharmacodynamic profile and between-subject variability of insulin detemir in subjects with type 1 diabetes (Abstract). *Diabetes*. 2002;51(2):53.
42. Klein O, Lynge J, Endahl L, et al. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. *Diabetes, Obesity and Metabolism*. 2007;9(3):290-299. doi: 10.1111/j.1463-1326.2006.00685.x
43. Heise T, Nosek L, Ronn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes*. 2004;53(6):1614-1620. doi: 10.2337/diabetes.53.6.1614
44. Russell-Jones D, Simpson R, Hylleberg B, et al. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with

type I diabetes mellitus using a basal-bolus regimen. *Clinical Therapeutics*. 2004;26(5):724-736. doi: 10.1016/S0149-2918(04)90072-0
45. Tone A, Iseda I, Higuchi C, et al. Comparison of insulin detemir and insulin glargine on glycemic variability in patients with type 1 and type 2 diabetes. *Experimental and clinical endocrinology & diabetes*. 2010;118(5):320-324. doi: 10.1055/s-0029-1243230
46. Heller S, Kim H, Draeger E. Within-person variation in fasting blood glucose is correlated to incidence of hypoglycaemia in people with Type 1 diabetes treated with insulin detemir and NPH insulin [abstract]. *Diabetologia*. 2004;47(1):303.
47. Vague P, Selam J-L, Skeie S, et al. Insulin Detemir Is Associated With More Predictable Glycemic Control and Reduced Risk of Hypoglycemia Than NPH Insulin in Patients With Type 1 Diabetes on a Basal-Bolus Regimen With Premeal Insulin Aspart. *Diabetes care*. 2003;26(3):590-596. doi: 10.2337/diacare.26.3.590
48. De Leeuw I, Vague P, Selam JL, et al. 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, Obesity and Metabolism*. 2005;7(1):73-82. doi: 10.1111/j.1463-1326.2004.00363.x
49. Raslova K, Bogoev M, Raz I, et al. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes research and clinical practice*. 2004;66(2):193-201. doi: 10.1016/j.diabres.2004.03.003
50. Tschritter O, Schafer SA, Klett J, et al. Insulin detemir causes increased symptom awareness during hypoglycaemia compared to human insulin. *Diabetes, obesity & metabolism*. 2009;11(11):1017-1026. doi: 10.1111/j.1463-1326.2009.01085.x
51. Fleischer J. Diabetic autonomic imbalance and glycemic variability. *Journal of diabetes science and technology*. 2012;6(5):1207-1215. doi: 10.1177/193229681200600526
52. Standl E, Schnell O, Ceriello A. Postprandial Hyperglycemia and Glycemic Variability: Should we care? *Diabetes care*. 2011;34(Suppl 2):S120-S127. doi: 10.2337/dc11-s206
53. Chang TI, Horal M, Jain SK, et al. Oxidant regulation of gene expression and neural tube development: Insights gained from diabetic pregnancy on molecular causes of neural tube defects. *Diabetologia*. 2003;46(4):538-545. doi: 10.1007/s00125-003-1063-2
54. Li R, Chase M, Jung SK, et al. Hypoxic stress in diabetic pregnancy contributes to impaired embryo gene expression and defective development by inducing oxidative stress. American journal of physiology *Endocrinology and metabolism*. 2005;289(4):E591-599. doi: 10.1152/ajpendo.00441.2004
55. Agarwal A, Aponte-Mellado A, Premkumar BJ, et al. The effects of oxidative stress on female reproduction: a review. *Reproductive biology and endocrinology*. 2012;10:49. doi: 10.1186/1477-7827-10-49
56. Siegelaar SE, Holleman F, Hoekstra JBL, DeVries JH. Glucose Variability; Does It Matter? *Endocrine reviews*. 2010;31(2):171-182. doi: 10.1210/er.2009-0021
57. Johnson E. Glycemic Variability in Type 2 Diabetes Mellitus. In: Ahmad S, editor. Diabetes. *Advances in Experimental Medicine and Biology*. New York: Springer; 2013. p. 139-154. doi: 10.1007/978-1-4614-5441-0_13
58. Hartman I. Insulin analogs: impact on treatment success, satisfaction, quality of life, and adherence. *Clinical medicine & research*. 2008;6(2):54-67. doi: 10.3121/cmr.2008.793
59. International Diabetes Federation Clinical Guidelines Task Force. *Global Guideline on Pregnancy and Diabetes*. Brussels, Belgium: International Diabetes Federation; 2009. Available at: http://www.idf.org/global-guideline-pregnancy-and-diabetes.
60. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA*. 2009;301(6):636-650. doi: 10.1001/jama.2009.113
61. Ramachenderan J, Bradford J, McLean M. Maternal obesity and pregnancy complications: a review. *The Australian & New Zealand journal of obstetrics & gynaecology*. 2008;48(3):228-235. doi: 10.1111/j.1479-828X.2008.00860.x
62. Dennedy MC, Avalos G, O'Reilly MW, et al. The impact of maternal obesity on gestational outcomes. *Irish medical journal*. 2012;105(5 Suppl):23-25.
63. Schieve L, Cogswell M, Scanlon K. Trends in Pregnancy Weight Gain Within and Outside Ranges Recommended by the Institute of Medicine in a WIC Population. *Matern Child Health J*. 1998;2(2):111-116. doi: 10.1023/A:1022992823185
64. Most O, Langer O. Gestational diabetes: maternal weight gain in relation to fetal growth, treatment modality, BMI and glycemic control. *The journal of maternal-fetal & neonatal medicine*. 2012;25(11):2458-2463. doi: 10.3109/14767058.2011.650250
65. Brown JE, Murtaugh MA, Jacobs DR, Jr., Margellos HC. Variation in newborn size according to pregnancy weight change by trimester. *The American journal of clinical nutrition*. 2002;76(1):205-209.
66. Gestational Diabetes Mellitus. Diabetes care. 2004;27(suppl 1):s88-s90. doi: 10.2337/diacare.27.2007.S88.
67. Rae A, Bond D, Evans S, et al. A randomised controlled trial of dietary energy restriction in the management of obese women with gestational diabetes. *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 2000;40(4):416-422. doi: 10.1111/j.1479-828X.2000.tb01172.x
68. Tanentsapf I, Heitmann BL, Adegboye ARA. Systematic review of clinical trials on dietary interventions to prevent excessive weight gain during pregnancy among normal weight, overweight and obese women. *BMC Pregnancy and Childbirth*. 2011;11:81-81. doi: 10.1186/1471-2393-11-81
69. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes – causes, effects and coping strategies. *Diabetes, Obesity and Metabolism*. 2007;9(6):799-812. doi: 10.1111/j.1463-1326.2006.00686.x
70. Home P, Bartley P, Russell-Jones D, et al. Insulin Detemir Offers Improved Glycemic Control Compared With NPH Insulin in People With Type 1 Diabetes: A randomized clinical trial. *Diabetes care*. 2004;27(5):1081-1087. doi: 10.2337/diacare.27.5.1081
71. Hermansen K, Davies M, Derezinski T, et al. A 26-Week, Randomized, Parallel, Treat-to-Target Trial Comparing Insulin Detemir With NPH Insulin as Add-On Therapy to Oral Glucose-Lowering Drugs in Insulin-Naïve People With Type 2 Diabetes. *Diabetes care*. 2006;29(6):1269-1274. doi: 10.2337/dc05-1365
72. Hordern SVM, Wright JE, Umpleby AM, et al. Comparison of the effects on glucose and lipid metabolism of equipotent doses of insulin detemir and NPH insulin with a 16-h euglycaemic clamp. *Diabetologia*. 2005;48(3):420-426. doi: 10.1007/s00125-005-1670-1
73. Hallschmid M, Jauch-Chara K, Korn O, et al. Euglycemic Infusion of Insulin Detemir Compared With Human Insulin Appears to Increase Direct Current Brain Potential Response and Reduces Food Intake While Inducing Similar Systemic Effects. *Diabetes*. 2010;59(4):1101-1107. doi: 10.2337/db09-1493
74. Zachariah S, Sheldon B, Shojaee-Moradie F, et al. Insulin Detemir Reduces Weight Gain as a Result of Reduced Food Intake in Patients With Type 1 Diabetes. *Diabetes care*. 2011;34(7):1487-1491. doi: 10.2337/dc11-0098
75. Руяткина Л.А., Сорокин М.Ю. Детемир (Левемир): современные парадигмы инсулинотерапии. // Проблемы эндокринологии. – 2013. – Т. 59. – №4. – С.56-64. [Ruiatkina LA, Sorokin MI. Detemir (Levemir): modern paradigms of insulin therapy. *Probl Endokrinol (Mosk)*. 2013;59(4):56-64. (In Russ).] doi: 10.14341/probl201359456-64.
76. Hyperglycemia and Adverse Pregnancy Outcomes. *New England Journal of Medicine*. 2008;358(19):1991-2002. doi: 10.1056/NEJMoa0707943
77. Дедов И.И., Краснопольский В.И., Сухих Г.Т. Российский национальный консенсус «Гестационный сахарный диабет: диагностика, лечение, послеродовое наблюдение». // Сахарный диабет. – 2012. – Т. 15. – №4 – С.4-10. [Dedov II, Krasnopol'skiy VI, Sukhikh GT. Russian National Consensus Statement on gestational diabetes: diagnostics, treatment and postnatal care. *Diabetes mellitus*. 2012;15(4):4-10 (In Russ).] doi: 10.14341/2072-0351-5531
78. Lapolla A, Dalfrà MG, Ragazzi E, et al. New International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommendations for diagnosing gestational diabetes compared with former criteria: a retrospective study on pregnancy outcome. *Diabetic Medicine*. 2011;28(9):1074-1077. doi: 10.1111/j.1464-5491.2011.03351.x
79. Nachum Z, Ben-Shlomo I, Weiner E, Shalev E. Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy: randomised controlled trial. *BMJ*. 1999;319(7219):1223-1227. doi: 10.1136/bmj.319.7219.1223
80. Lapolla A, Di Cianni G, Bruttomesso D, et al. Use of insulin detemir in pregnancy: a report on 10 Type 1 diabetic women. *Diabetic Medicine*. 2009;26(11):1181-1182. doi: 10.1111/j.1464-5491.2009.02852.x
81. Sciacca L, Marotta V, Insalaco F, et al. Use of insulin detemir during pregnancy. *Nutrition, Metabolism and Cardiovascular Diseases*. 2010;20(4):e15-e16. doi: 10.1016/j.numecd.2009.12.010
82. Kurtzhals P, Schäffer L, Sørensen A, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes*. 2000;49(6):999-1005. doi: 10.2337/diabetes.49.6.999
83. Hod M, Mathiesen ER, Jovanovič L, et al. A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2014;27(1):7-13. doi: 10.3109/14767058.2013.799650
84. Mathiesen ER, Hod M, Ivanisevic M, et al. Maternal Efficacy and Safety Outcomes in a Randomized, Controlled Trial Comparing Insulin Detemir With NPH Insulin in 310 Pregnant Women With Type 1 Diabetes. *Diabetes care*. 2012;35(10):2012-2017. doi: 10.2337/dc11-2264
85. Hod M, Damm P, Kaaja R, et al. Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. *American Journal of Obstetrics & Gynecology*. 2008;198(2):186.e181-186.e187. doi: 10.1016/j.ajog.2007.08.005

86. *Pregnancy in women with type 1 and type 2 diabetes 2002–2003: England, Wales and Northern Ireland: executive summary* [PDF online]. London: CEMACH; 2005. Available from http://www.bathdiabetes.org/resources/254.pdf. Accessed 18 May 2012

Информация об авторах [Authors Info]

Руяткина Людмила Александровна, д.м.н., профессор [Ludmila A. Ruyatkina, MD, PhD, Professor]. Адрес: 630091, г.Новосибирск, Красный проспект, д. 52. [Address: 52, Krasny prospect, Novosibirsk, 630099 Russian Federation]; eLibrary SPIN: 1895-7664. Email: larut@list.ru.

Сорокин Максим Юрьевич [Maksim Y. Sorokin, MD].

Цитировать:

Руяткина Л.А., Сорокин М.Ю. Возможности применения инсулина детемир при лечении сахарного диабета у беременных: доказанные преимущества и перспективы использования // Сахарный диабет. — 2016. — Т.19. — №2. — С. 171-178. doi: 10.14341/DM2004130-33

To cite this article:

Ruyatkina LA, Sorokin MY. Potential applications of detemir in the treatment of diabetes during pregnancy: proven benefits and perspectives. *Diabetes Mellius.* 2016;19(2):171-178. doi: 10.14341/DM2004150-55