В последние годы наблюдается рост распространенности гестационного и манифестного сахарного диабета (СД) у беременных женщин при сохраняющемся высоком уровне акушерских осложнений, 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 достичь 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

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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
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/ultrashort-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 hypoglycaemia 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
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 hunger and satiety, hypoglycaemia 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 hyperglycaemia; high doses of insulin are required to manage insulin resistance in some cases, which is accompanied by higher risk of hypoglycaemia.

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 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].

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).
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 the entire course of 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.

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