Toward Implementation of the Saint Vincent Declaration: Outcomes of Women with Pregestational Diabetes

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ABSTRACT: **Background:** Pregestational diabetes mellitus (PGDM) carries a significantly elevated risk of adverse maternal and fetal outcomes. There is evidence that certain interventions reduce the risk for adverse outcomes. Studies have shown that a multi-disciplinary approach improves pregnancy outcomes in women with PGDM.

Objectives: To determine pregnancy outcomes in women with PGDM using a multi-disciplinary approach.

Methods: We retrospectively reviewed consecutive women with pregestational type 1 and type 2 diabetes who were monitored at a high-risk pregnancy clinic at the Sheba Medical Center. Clinical data were obtained from the medical records. All data related to maternal glucose control and insulin pump function were prospectively recorded on Medtronic CareLink® pro software (Medtronic MiniMed, Northridge, CA).

Results: This study comprised 121 neonates from 116 pregnancies of 94 women. In 83% of the pregnancies continuous glucose monitoring (CGM) sensors were applied during a part or all of the pregnancy. Pregnancy outcomes among women who were followed by a multi-disciplinary team before and during pregnancy, and during labor and puerperium resulted in better glucose control (hemoglobin A1c 6.4% vs. 7.8%), lower risk for pregnancy induced hypertension/ preeclampsia (7.7% vs. 15.6%), lower birth weight (3212 grams vs. 3684 grams), and lower rate of large size for gestational age and macrosomia (23.1% vs. 54.2% and 3.3% vs. 28.4%, respectively), compared to data from European cohorts.

Conclusions: The multi-disciplinary approach for treating women with PGDM practiced in the high-risk pregnancy clinic at the Sheba Medical Center resulted in lower rates of macrosomia, LGA, and pregnancy induced hypertension compared to rates reported in the literature.

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KEY WORDS: large for gestational age (LGA), multidisciplinary approach, pregestational diabetes mellitus (PGDM), pregnancy complications, type 1 diabetes

In 1989, the Saint Vincent Declaration set a 5-year target for approximating outcomes of pregnancies in women with diabetes to those of the background population [1]. Despite an improvement in recent years, the risk of adverse pregnancy outcomes is still twofold to fivefold higher in women with type 1 diabetes mellitus (T1DM) compared to the general population. There is an increased risk for congenital malformations (relative risk [RR] = 2.4), perinatal mortality (RR = 3.7), preterm delivery (RR = 4.2), and delivery of large for gestational age (LGA) infants (RR = 4.5) [2]. Moreover, there is a higher risk for macrosomia (RR = 4.5), pre-eclampsia (RR = 12.1), Cesarean section (RR = 3.7), and maternal mortality (RR = 60.0) even with suitable glycemic control [3]. Long-term adverse effects have also been reported, such as elevated risk for overweight in adolescent children of PGDM (RR = 1.7) [4].

There is evidence that certain interventions reduce the risk for adverse pregnancy outcomes. These include pre-pregnancy care [5], folic acid supplementation [6], pre-conceptional and gestational glycemic control [7,8], and nutritional support for managing gestational weight gain [9]. Regional pregestational diabetes multi-disciplinary clinics (including an obstetrician, a diabetes expert physician, a dietitian, and nurses), which provide integrative care with routine appointments every 2 weeks, have been shown to reduce risk of adverse pregnancy outcome in pregestational diabetes (PGDM) [9,10]. In a study from England, a 1.3% rate of adverse pregnancy outcomes in women with diabetes attending pregestational care versus 7.8% in the general population with diabetes was reported [5]. In a study from Ireland, an increase in attendance rate in the pre-pregnancy care clinic (23–49%) was associated with a reduction in congenital malformations and stillbirths rates (5%–1.8%, $P = 0.04$, and 2.3–0.4%, $P = 0.09$, respectively) [10].

In the high-risk pregnancy clinic at the Sheba Medical Center, a multi-disciplinary team, which included an endocrinologist, perinatologist, dietitian, and nurses, treated women with PGDM. The women were followed before pregnancy to ensure adequate glucose control before conception, during pregnancy every 1–2 weeks, and during labor and puerperium with frequent adjustment of insulin doses and education regarding the use of technology (pump, continues glucose monitoring, bolus calculator, low glucose suspend), nutrition, and physical activity.

The aim of this study was to determine pregnancy outcomes using this multi-disciplinary approach and to

compare pregnancy complications rates in our cohort (the Pre-pregnancy Diabetes Cohort Study [PDSC]) to rates reported in the literature.

PATIENTS AND METHODS

STUDY DESIGN

This study was designed to be a historical prospective. The study included consecutive women with pregestational T1DM and type 2 diabetes mellitus (T2DM) who were monitored before and/or during pregnancy at the high-risk pregnancy clinic and delivered at the Sheba Medical Center or at other hospitals in which data regarding neonatal and maternal outcomes were available. Continuous glucose monitoring (CGM) sensors are included in the Israeli public medical insurance for pregnant women with diabetes, and thus are provided free of charge to this population. In 97/116 pregnancies (83%) CGM was used during the whole pregnancy or part of it, with a median usage of 6 weeks. All clinical data were recorded on the hospital computerized comprehensive database. All data related to maternal glucose control and insulin pump function were recorded on Medtronic CareLink® pro software (Medtronic MiniMed, Northridge, CA, USA). Data from these databases were joined and coded. This study was approved by the Sheba Institute institutional review board committee, approval number 3004-16-SMC.

TREATMENT OF WOMEN WITH PGDM IN THE SHEBA MEDICAL CENTER HIGH-RISK CLINIC

The multi-disciplinary clinic for women with PGDM included a dedicated nurse, perinatologist, endocrinologist, and dietician. All women were advised to attend pre-pregnancy counseling. Tight glucose control prior to pregnancy was highly recommended as well as high dose folic acid supplementation and frequent follow-up visits. During pregnancy women attended the multi-disciplinary clinic every 2 weeks until 31 weeks of gestations and thereafter every week.

At the first visit a full medication review was performed, followed by prescriptions for pregnancy-appropriate medications on an individual basis. Recommendations for alcohol and smoking cessation were provided. Thyroid functions were assessed and appropriately managed. Screening for renal, retinal, neurological, or cardiovascular diabetes complications was performed. A retinal evaluation was performed every trimester or when necessitated clinically, and proper management of hypoglycemia was discussed. The women were instructed to perform self-capillary blood glucose monitoring at least seven times daily: at arousal, pre-prandial, one hour postprandial, at bed-time, and if suspected hyper/hypo glycemia. All women were encouraged to use CGM, which is provided free of charge to women with PGDM in Israel. Body mass index (BMI) was calculated at each clinic attendance and weight gain was strictly monitored. Physical activity was encouraged, and a balanced diet was advised by a professional dietician. Glucose control was achieved using multiple daily injections or pump. Women were encouraged to use the pump technology.

During each visit to the clinic, data regarding maternal glycemic control and basal bolus insulin doses were reviewed by the endocrinologist and dietitian and appropriate changes in insulin doses were made. Patient education regarding proper use of technology (insulin pump, continues glucose monitoring, bolus calculator use, and low glucose suspend features) for optimal glucose control was emphasized. The hemoglobin A1C (A1C) levels were measured, and blood and urine analysis were routinely performed.

An ultrasound scan was performed to confirm gestational age and viability. Thereafter, fetal growth and amniotic fluid index were evaluated at every clinic attendance. A decision regarding time and mode of delivery was made on an individual basis, considering the patient's glycemic control, obstetrical complications, the estimated fetal weight, and fetal markers of wellbeing. During the third trimester women were encouraged to remain with the pump during delivery and were provided with a specialized tailored-made protocol for changes in insulin doses during delivery.

During the immediate postpartum period, breastfeeding was highly recommended. All of the women were evaluated by an endocrinologist prior to discharge; their insulin requirements were reviewed and changed appropriately. Women were encouraged to continue glucose monitoring and to return to their pregestational BMI. All women attended the clinic 6 weeks after delivery for thorough evaluation, contraception counseling, and continuous medical guidance.

DEFINITION OF VARIABLES

Diabetes microvascular complications were defined as a composite of any degree of retinopathy, neuropathy, or nephropathy. Gestational hypertension was defined as a systolic pressure > 140 mmHg or a diastolic pressure > 90 mmHg, without proteinuria, on at least two occasions more than 6 hours apart, in women with normal baseline blood pressure. Pre-eclampsia was defined as onset of gestational hypertension with proteinuria > 300 mg/L in 24 hours. Preterm delivery was defined as delivery before 37 completed gestational weeks. Large for gestational age (LGA) was defined as birth weight above 90th birth percentile and small for gestational age (SGA) as birth weight below 10th birth percentile, according to national birth percentile charts standardized for gestational age, sex, and singleton versus multiple delivery [11]. Fetal macrosomia was defined as fetal weight > 4 kg at birth. Clinically significant neonatal hypoglycemia was defined as hypoglycemia requiring intravenous (IV) glucose treatment.

STATISTICAL ANALYSIS

Data regarding glucose control indices (including A1C, mean capillary/CGM glucose levels [mg/dl]) and standard deviation (SD) of mean glucose levels (mg/dl) were reported for each 6 week interval, starting 12 weeks before the last menstruation date until 6 weeks after delivery. Continuous variables were summarized using means with SD. Binary/categorical variables were summarized using counts and percentages.

Table 1. Cohort characteristics

Age at pregnancy (years)	32.5 ± 5.6
Diabetes type	
T1DM	108 (89.3)
T2DM	11 (9.1)
Other	2 (1.6)
Years of diabetes	14.1 ± 7.9
Years with insulin pump	6.7 ± 6.1
Microvascular complications*	19 (15.7)
HbA1c	
Pregestational	6.8 ± 1.1
First trimester	6.4 ± 0.7
Second trimester	5.8 ± 0.6
Third trimester	5.9 ± 0.6
Hypertension	4 (3.3)
Dyslipidemia	23 (19.0)
Hypothyroidism	53 (43.8)
Grave's disease	3 (2.5)
BMI before pregnancy	25.1 ± 4.7
Gestational weight gain (kg)	12.1 ± 4.5
Gravity	2.8 ± 2.4
Parity	1.3 ± 1.8

Dichotomous variables are reported as N (%), continuous variables are reported as mean ± SD

*Complications include retinopathy, neuropathy, or nephropathy

BMI = body mass index, HbA1c = hemoglobin A1c, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus

RESULTS

Between April 2011 and December 2017, 124 neonates were born to 94 consecutive PGDM women attending the high-risk pregnancy clinic at the Sheba Medical Center. In the analysis, 121 neonates (98%) were included. Data for three neonates (2%) were not included in the analysis as outcome data were not available. During the study period, 77 women delivered once, 13 delivered twice, 3 delivered three times; and one woman delivered four times; and 5 women delivered twins. The CGM sensors were used by 97 women (80%) during their pregnancy. Table 1 presents the characteristics of the women. Mean age at the beginning of pregnancy was 32.5 years (± 5.6), 89.3% of the patients had pregestational type 1 diabetes with mean disease duration of 14.1 years (± 7.9) and 15.7% had microvascular disease. An insulin pump was used in 97.5% of the pregnancies and a CGM in 83.6%.

GLYCEMIC CONTROL

Data regarding glucose control indices are presented in Table 2. As pregnancy progressed, there was a reduction in A1C, mean glucose levels, and mean standard deviations of glucose levels.

PREGNANCY OUTCOMES

The average delivery was at week 37+ 5 (± 7 days): 28 of 121 neonates (23.1%) were delivered pre-term: 15 of 121 neonates (12.4%) were born preterm due to maternal or neonatal grounds, such as non-reassuring fetal monitor, pre-eclamptic toxemia (PET), or impending macrosomia. Only 13 of 121 neonates (10.7) were delivered spontaneously preterm, among them 3 sets of twins. Of the 28 preterm delivered neonates only 4 (3.3%) were delivered before completion of 34 full gestational weeks. None were delivered before completion of 32 full gestational weeks. In total, 67 (55.4%) neonates were vaginally delivered, of those 7 (5.7%) with instrumental delivery, and 54 (44.6%) were born by Cesarean section. There were 2 (1.7%) patients with postpartum hemorrhage.

Table 2. Glycemic control indices: results

	Pre-conception		1st trimester		2nd trimester		3rd trimester		Postpartum
	‹ 12 weeks	‹ 6 weeks	0–7 weeks	7–13 weeks	14–20 weeks	21–26 weeks	27–33 weeks	34 weeks – delivery	+6 weeks
HbA1c (%) (N=121)	6.78 ± 1.05	6.76 ± 1.05	6.55 ± 1.01	6.32 ± 0.77	5.88 ± 0.68	5.76 ± 0.67	5.81 ± 0.62	5.96 ± 0.63	6.37 ± 0.82
Mean glucose (mg/dl) (n=121)	132.94 ± 27.59	139.82 ± 28.99	139.89 ± 26.46	121.51 ± 22.57	116.14 ± 16.53	121.63 ± 16.37	124.84 ± 17.61	117.02 ± 118.56	127.29 ± 22.74
SD of mean glucose (mg/dl) (n=121)	59.08 ± 23.20	58.01 ± 22.63	60.26 ± 18.46	52.81 ± 16.60	49.32 ± 13.20	49.34 ± 13.77	47.46 ± 11.34	44.99 ± 10.56	56.74 ± 16.66
Mean sensor glucose (mg/dl) (n=95)	122.90 ± 16.90	117.00 ± 29.20	128.40 ± 20.80	112.90 ± 16.30	111.10 ± 14.80	116.10 ± 13.90	121.40 ± 17.30	111.40 ± 15.00	118.60 ± 19.70
SD of mean sensor glucose (mg/dl) (n=95)	42.80 ± 12.78	42.27 ± 17.05	48.93 ± 11.92	44.84 ± 9.39	43.19 ± 9.75	44.51 ± 10.63	44.46 ± 10.78	40.61 ± 9.77	45.97 ± 10.57

*Continuous variables are reported as mean ± SD

HbA1c = hemoglobin A1c, SD = standard deviation

During pregnancy there were no cases of diabetic ketoacidosis. In 10 pregnancies at least one severe hypoglycemic event requiring the aid of another person was experienced (8.6%), and one woman experienced hypoglycemic coma (0.8%). Four pregnancies (3.4%) were complicated by gestational hypertension; five (4.3%) were complicated by PET; and one (0.8%) by HELLP syndrome [Table 3, Figure 1].

NEONATAL OUTCOMES

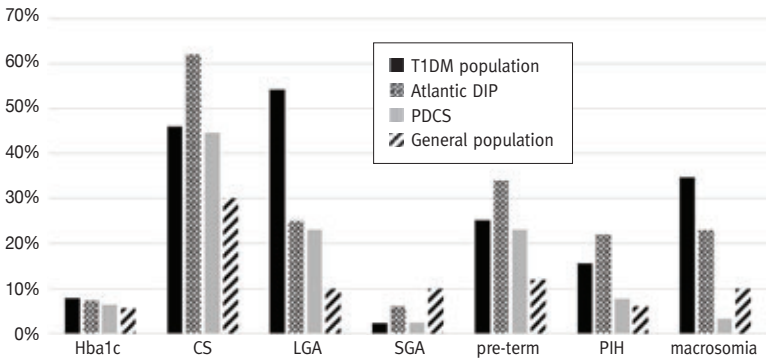
There were no cases of intra-uterine fetal death. Average birth weight and average birth percentile were 3212.41 ± 532.79 g and 66.90%, respectively. Table 3 and Figure 1 present pregnancy outcomes. Twenty-eight neonates (23.1%) were LGA with four (3.3%) of them defined as macrosomic and 3 neonates (2.5%) were SGA. Regarding complications, 17 neonates (14%) required phototherapy for hyperbilirubinemia, 5 neonates (4.1%) were diagnosed with respiratory distress syndrome, 8 neonates (6.6%) with transient tachypnea of the newborn, and 7 neonates (5.8%) had meconium stained amniotic fluid. Congenital anomalies were observed in 5 neonates (4.1%): 4 (3.3%) had ventricular septal defect and 1 (0.8%) had clubfoot. Two deliveries (1.6%) were complicated by shoulder dystocia and a fractured clavicle of one neonate without Erb's palsy. Five neonates (4.1%) had an Apgar score at 1 minute of less than 7. At 5 minutes only one (0.8%) of these neonates had an Apgar score of less than 7. Intravenous glucose treatment was required by 32 neonates (27.6%) experienced hypoglycemia.

Table 3. Worldwide comparison of pregnancy outcome results

	T1DM population	Atlantic DIP	Pre-pregnancy Diabetes Cohort Study	General population
1st trimester HbA1c	7.8%**	6.7%–7.3%	6.4%	5.7%
Congenital malformations	5%[#]	1.8%	4.1%	2.1%
Stillbirth	0.72%[#]	0.4%	0%	~0.006%
Cesarean section	46%[§]	62%	44.6%	~30%
Pregnancy induced hypertension or preeclampsia	15.6%[§]	22%	7.7%	6%
Average birth weight (gram)	3684[§]	3500 ± 850	3212 ± 533	~3500
Macrosomia	28.4–34.7%[§]	23%	3.3%	1.5%
Neonatal hypoglycemia	~48%[‡]	12%	27.6%	3–29%
Shoulder dystocia	2.1%[§]	1.4%	1.6%	~0.5%
LGA	46.4%*–54.2%[#]	25%	23.1%	10%
SGA	2.3%[§]	6%	2.5%	10%
Preterm delivery	25.2%[#]	34%	23.1%	12%

*Data from Murphy et al. [11]
**Data from Glinianaia et al. [15]
[#]Data from Colstrup et al. [2]
[§]Data from Persson et al. [16]
[‡]Data from Harris et al. [17]
DIP = diabetes in pregnancy, LGA = large for gestational age, SGA = small for gestational age, T1DM = type 1 diabetes mellitus

Figure 1. Worldwide comparison of pregnancy outcome results



CS = cesarean section, DIP = diabetes in pregnancy, HbA1c = hemoglobin A1c, LGA = large for gestational age, PDCS = Pre-pregnancy diabetes cohort study, PIH = Pregnancy induced hypertension, SGA = small for gestational age, T1DM = type 1 diabetes mellitus

DISCUSSION

Compared to the general population with diabetes, pregnancy outcomes among women who were followed by a multi-disciplinary team, resulted in better glucose control (A1C of 6.4% [46.4 mmol/mol] vs. 7.8% [61.7 mmol/mol]), a lower risk for pregnancy induced hypertension/PET (7.7% vs. 15.6%), and lower rates of LGA and macrosomia (23.1% vs. 54.2%, and 3.3% vs. 28.4%, respectively) [Table 3, Figure1].

Other studies reported similar results. The Atlantic Diabetes in Pregnancy (DIP) program, which provides care to women with PGDM in Ireland and includes a structured regional pre-pregnancy care program and regional multi-disciplinary antenatal diabetes clinics reported similar results among 228 pregnant women (61% T1DM, 39% T2DM) followed in their program [10]. The authors reported a mean first trimester A1C of 7.3% [56.3 mmol/mol] in T1DM and 6.7% [49.7 mmol/mol] in T2DM, a 1.8% rate of overall congenital malformations, 22% of pregnancy-induced hypertension (PIH), 34% of preterm delivery, 1.4% of shoulder dystocia, 23% of macrosomia, 25% of LGA, 6% of SGA, and 12% of neonatal hypoglycemia.

As described by Murphy et al. [12], there is substantial variation in pregnancy outcomes across clinics, suggesting that the impact of clinic context is also important. There may be several reasons for the better pregnancy outcomes reported in our cohort versus data reported for the general PGDM population. First, it may be that women attending a high-risk tertiary referral clinic are either at lower risk for adverse outcomes or may be more motivated. Thus, the lower rates of adverse outcomes observed may be attributed to general better health or better health care behaviors. However, in Israel women are generally treated in high-risk pregnancy clinics in the community and only the more severe cases are referred from their health maintenance organization (HMO) to a hospital setting, thus this is probably not a sole explanation. Second, it may be that

the multi-disciplinary approach that includes patient education starting before conception includes proper use of technology (insulin pump, continues glucose monitoring, bolus calculator use, and low glucose suspend features) for optimal glucose control, and frequent follow-up visits contributed to the lower rate of adverse outcomes. This result may be due partly to better glucose control achieved before, during pregnancy, and at childbirth; better adherence to folic acid supplementation; balanced gestational weight gain [13]; administration of low dose aspirin for reducing risk of hypertensive pregnancy complications; appropriate administration of steroids for fetal lung maturation; change in glucose control regimen according to ultrasound estimation of fetal growth and amniotic fluid index (which are evaluated at every clinic attendance); and individualized decision regarding timing and need of induction of labor taking into account the woman's glycemic control, obstetrical complications and the estimated fetal weight and fetal markers of wellbeing.

LIMITATIONS

This cohort is a sample of consecutive women attending the high-risk pregnancy clinic at a tertiary referral center. It is not clear whether these results may be generalized to other patient populations. Indeed, in Israel women with pregestational diabetes are generally treated in their respective HMOs and only the more severe cases are referred to the hospital. Second, pregnancy outcomes were reported for the cohort and compared with results reported in the literature without comparison to standard of care in Israel. Thus, it is hard to discern which part of the approach described above contributed to the results. The data presented can, however, serve as a bench-mark for obtainable outcomes in PGDM.

The multi-disciplinary approach presented here takes place at a tertiary referral clinic. However, to be relevant for as many patients as possible, it should be established within the frame of community medicine. Moreover, it has been shown that ambulatory care is as effective as hospitalization among PGDM patients with regard to glycemic control and neonatal morbidity. Therefore, expanding this approach to a designated community clinic will not only be more convenient for the patient, but could significantly reduce treatment costs [14].

CONCLUSIONS

We reported the pregnancy outcomes of women treated by a multi-disciplinary team with pre-pregnancy counseling, frequent follow-up including during labor and puerperium with tight glycemic control, and frequent use of diabetes technology. Compared to the literature we reported lower rates of macrosomia, LGA, and PIH. Further prospective studies are needed to validate these results and test if they may be applicable on a larger scale.

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References

1. Diabetes Care and Research in Europe: The Saint Vincent Declaration. *Diabet Med* 1990; 7: 360.
2. Colstrup M, Mathiesen ER, Damm P, Jensen DM, Ringholm L. Pregnancy in women with type 1 diabetes: have the goals of St. Vincent Declaration been met concerning foetal and neonatal complications? *J Matern Fetal Neonatal Med* 2013; 26 (17): 1682-6.
3. 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.
4. Farfel A, Merdler-Rabinowicz R, Abebe-Campino G, Derazne E, Laron-Kenet T, Laron Z. Risk of overweight in adolescence among offspring of diabetic mothers. *IMAJ* 2017; 19 (5): 275-6.
5. Murphy HR, Roland JM, Skinner TC, et al. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes. *Diabetes Care* 2010; 33 (12): 2514-20.
6. Correa A, Gilboa SM, Botto LD, et al. Lack of peri-conceptional vitamins or supplements that contain folic acid and diabetes mellitus-associated birth defects. *Am J Obstet Gynecol* 2012; 206 (3): 218. e1-218.
7. Middleton P, Crowther CA, Simmonds L, Muller P. Different intensities of glycaemic control for pregnant women with pre-existing diabetes. *Cochrane Database Syst Rev* 2010; 9.
8. Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Avalos G, Dunne F. ATLANTIC-DIP: excessive gestational weight gain and pregnancy outcomes in women with gestational or pregestational diabetes mellitus. *J Clin Endocrinol Metab* 2014; 99 (1): 212-9.
9. Owens LA, Egan AM, Carmody L, Dunne F. Ten years of optimizing outcomes for women with type 1 and type 2 diabetes in pregnancy—the Atlantic DIP experience. *J Clin Endocrinol Metab* 2016; 101 (4): 1598-605.
10. Dollberg S, Haklai Z, Mimouni FB, Gorfein I, Gordon ES. Birth weight standards in the live-born population in Israel. *IMAJ* 2005; 7 (5): 311-4.
11. Ben YN, Chermesh I, Solt I, Friedrich Y, Lowenstein L. Achieving the recommended gestational weight gain in high-risk versus low-risk pregnancies. *IMAJ* 2018; 20 (7): 411-4.
12. Nachum Z, Ben-Shlomo I, Weiner E, Ben-Ami M, Shalev E. Diabetes in pregnancy: efficacy and cost of hospitalization as compared with ambulatory management–a prospective controlled study. *IMAJ* 2001; 3 (12): 915-9.
13. Glinianaia SV, Tennant PWG, Bilous RW, Rankin J, Bell R. HbA1c and birthweight in women with pre-conception type 1 and type 2 diabetes: a population-based cohort study. *Diabetologia* 2012; 55 (12): 3193-203.
14. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies. *Diabetes Care* 2009; 32 (11): 2005-9.
15. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. *J Pediatr* 2012; 161 (5): 787-91.

"Smaller than a breadbox, bigger than a TV remote, the average book fits into the human hand with a seductive nestling, a kiss of texture, whether of cover cloth, glazed jacket, or flexible paperback"

John Updike (1932–2009), writer