Quality of Medical Care in Diabetic Women Undergoing Fertility Treatment

We should do better!

SHLOMIT RISKIN-MASHIAH, MD
RON AUSLANDER, MD

OBJECTIVE—Diabetic women are at increased risk for adverse pregnancy outcomes that can be improved by preconception care. Our goal was to evaluate the quality of medical care in diabetic women who undergo fertility treatment and compare it with the quality of medical care in diabetic women with spontaneous pregnancies.

RESEARCH DESIGN AND METHODS—This retrospective study on reproductive-age women undergoing fertility treatment in Clalit Health Services (CHS) used data on fertility treatments, prescription fillings, HbA_{1c} levels, and demographics extracted from CHS computerized systems. The control group comprised women with spontaneous pregnancy. Three quality measures in the periconception period were evaluated: folic acid prescription fillings, evaluation and level of HbA_{1c}, and use of potentially hazardous drugs.

RESULTS—There were 230 fertility treatment cycles in 83 diabetic women, and 30 diabetic women had spontaneous pregnancy. Women in the fertility group were older and had fewer children. There were no significant differences in marital status or ethnicity. Regular folic acid use, HbA_{1c} recording, and the percentage of women with HbA_{1c} <7% was similar between women in fertility treatment and those with spontaneous pregnancy (23.9, 57.8, and 31.3% vs. 20.0, 73.3, and 40.0%, respectively). Several women in both groups continued the use of potentially hazardous medication.

CONCLUSIONS—The periconception medical care of diabetic women who undergo fertility treatment is suboptimal and no better than that of diabetic women with spontaneous pregnancies. More intensive and targeted counseling regarding the importance of folic acid and glycemic control is needed to optimize periconception care of these diabetic patients.

Diabetes Care 34:2164–2169, 2011

Diabetes is a chronic disease with increasing incidence in recent years in parallel with the obesity epidemic. The growing prevalence of type 2 diabetes in general, and the advancing age of women in pregnancy, especially among those who undergo fertility treatment, has led to an increasing number of pregnancies with this complication (1). Pregestational diabetes raises the risk of pregnancy complications to the mother, fetus, and newborn infant. The duration and type of diabetes, its severity, the occurrence of chronic complications, and the level of glucose control are the major factors influencing pregnancy outcome (1,2). Poorly controlled pregestational diabetes substantially multiplies the risk of spontaneous abortion and congenital malformations (1–3). Many studies (2,3) and meta-analyses (4,5) show that women who get appropriate preconception care have significantly lower risk for adverse pregnancy outcomes, including spontaneous abortions, congenital malformations, and prolonged hospitalizations for mothers and neonates. For these reasons, societies around the world have published guidelines for preconception counseling for women with diabetes (6,7). All these guidelines recommend daily periconceptional use of folate supplementation to prevent neural tube defects; good metabolic control before conception, preferably with HbA_{1c} below 6–7%; and review of medication use and discontinuation, periconceptionally, of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), and statins. However, many spontaneous pregnancies are still unplanned, and many diabetic women get pregnant without proper preparation and with poor glycemic control and, thus, have high rates of pregnancy complications (8–11).

Unlike many unintended and unplanned pregnancies, couples with fertility problems yearn for a child, sometimes for years ahead. The infertile couple has made a conscious decision that they desire pregnancy and are thoroughly invested in optimizing the chances for a successful pregnancy outcome. Also, women who undergo fertility treatment are older and have more chronic medical diseases than average pregnant women. Thus, these women are an ideal group for preconception evaluation and counseling to ensure best outcome for mother and child, as recently stressed by the British inquiry into maternal deaths (12).

Therefore, our goal was to evaluate the quality of preconception medical care in diabetic women who undergo fertility treatment and compare it with the quality of medical care in diabetic women with spontaneous pregnancies.

RESEARCH DESIGN AND METHODS

—The study was approved by the ethics committee of Clalit Health Services (CHS). The protocol for computerized data retrieval was also approved by the committee for health policy research in the central administration of CHS. CHS is a nonprofit HMO covering more than half of the Israeli population. This is a retrospective study on reproductive-age women (17- to 55-years-old) undergoing fertility treatment during 2008–2009 in the Haifa and Western Galilee District of CHS in Israel.

Data on women undergoing fertility treatment were obtained from CHS pharmacies' computerized database using the following anatomic therapeutic

From the Department of Obstetrics and Gynecology, Lady Davis Carmel Medical Center, Rappaport Faculty of Medicine, Technion, Haifa, Israel.
Corresponding author: Shlomit Riskin-Mashiah, shlomitri@gmail.com.
Received 24 May 2011 and accepted 15 July 2011.
DOI: 10.2337/dc11-0966

chemical classifications: G03G (gonadotropins and other ovulation stimulants), H01CA (gonadotropin-releasing hormones [GnRH]), and L02AE (GnRH analogs). Usually, the prescriptions are given in advance for the entire treatment cycle, thus defining a fertility cycle. Fertility treatment was defined as the use of any of the following drugs either alone or in combinations: clomiphene citrate, gonadotropin, GnRH agonist, or GnRH antagonist. Women who received GnRH analogs alone for other indications (such as endometriosis or breast cancer) were omitted.

The control group was composed of women with spontaneous pregnancy who had started their prenatal care in the same district of CHS from 1 October 2008 to 31 March 2009.

Next, we extracted data from the CHS computerized systems on the following parameters for both groups of women: demographics, including date of birth, ethnicity, marital status, and number of children; all prescription fillings they made during the study period, including name of drug, dosage, quantity, and date of prescription filling; and dates and results of all HbA_{1c} tests that were done during the study period for women in both groups.

Diabetic patients were identified by either an $HbA_{1c} \geq 6.5\%$ (according to the American Diabetes Association recommendation for diabetes diagnosis) or prescription filling for oral hypoglycemic drug or insulin. Metformin is sometimes used in nondiabetic infertile women with polycystic ovary syndrome; thus, women who used metformin but no other antidiabetic drug were not categorized as having diabetes. We also excluded women with gestational diabetes only (based on prescription fillings for glibenclamide or insulin only during pregnancy or after fertility treatment).

Three measures of the quality of medical care in the periconception period were evaluated according to the preconception recommendations for women with diabetes (6,7). The first measure was folic acid prescription fillings (at any dose, including in multivitamins or in combination with iron) in the 3-month period prior to fertility treatment or pregnancy. Prescription fillings were calculated per month, according to the pill quantity in each prescription. Some folic acid formulas can be bought as over-the-counter drugs; yet all over-the-counter purchases are also recorded in the CHS pharmacies' computerized database. The second measure was evaluation of HbA_{1c} levels within 3 months of fertility treatment or pregnancy. HbA_{1c} levels in this time period represent the glycemic control in the periconception period and fetal organogenesis. And the third measure was use of potentially hazardous drugs (i.e., statins, ACE inhibitors, or ARBs) in the 1st month after fertility treatment or pregnancy.

Data were tested for normal distribution (Kolmogorov-Smirnov test); χ^2 test, *t* test, Mann-Whitney *U* test, and multivariate binary logistic regression analysis were conducted using SigmaStat version 2.03 and Minitab version 12.23; and statistical significance was set at $P < 0.05$.

RESULTS—There were 230 fertility treatment cycles in 83 diabetic women, and 30 diabetic women had spontaneous pregnancy during the study period. Women in the fertility group were older (36.8 ± 0.7 vs. 32.3 ± 1.1 years, $P = 0.001$) and had fewer children (median 1 vs. 2, $P < 0.001$). There were no significant differences in marital status (84 vs. 80% married) or ethnicity (43 vs. 57%, Jews, $P = 0.3$). Most women (55) received only one or two fertility treatment cycles during this 2-year period; the rest received up to eight treatment cycles. In 88 fertility cycles, clomiphene citrate was used either alone or in combination with human chorionic gonadotropin.

Folic acid prescription filling was similar in both groups; among the fertility group, in 104 fertility cycles (45.2%), at least one folic acid prescription was filled in the 3-month period prior to treatment compared with 16 women (53.3%) in the spontaneous pregnancy group (Table 1). Regular folic acid consumption was assumed if a woman filled >1 folic acid prescription in the 3-month period prior to fertility treatment or spontaneous pregnancy. Thus, in the fertility group, regular folic acid supplementation was used in only 55 fertility cycles (23.9%) compared with 6 women (20%) in the control group (Table 1).

HbA_{1c} level was recorded within 3 months of pregnancy in 22 (73%) women in the control group; in the infertility group, HbA_{1c} level was recorded within 3 months of treatment in 133 out of 230 cycles (57.8%), ($P = 0.15$). Median HbA_{1c} was also similar (6.7% in the control group vs. 7.0% in the fertility group) (Table 1). There was no significant difference in the percentage of women with good diabetic control ($HbA_{1c} < 7.0\%$), with 40% in the spontaneous pregnancy group compared with 31.3% in the fertility group ($P = 0.45$) (Table 1). Only 5 women (16.7%) with spontaneous pregnancy had excellent glycemic control with measured $HbA_{1c} \leq 6.0\%$ within 3 months of pregnancy, and 17 women in 35 fertility cycles (15.2%) had such an optimal HbA_{1c} recording. Moreover, 5 women in the control group and 10 women in 16 fertility cycles had a recorded $HbA_{1c} > 9.0\%$ within 3 months of pregnancy or fertility treatment. In summary,

Table 1—*Quality measures in women undergoing fertility treatment vs. spontaneous pregnancies*

Quality measure of preconception care	Fertility cycles ($n = 230$)	Spontaneous pregnancy ($n = 30$)	*P* value
At least one folic acid prescription filling in 3 months prior to fertility treatment or pregnancy	45.2	53.3	0.52
More than one folic acid prescription filling in 3 months prior to fertility treatment or pregnancy	23.9	20.0	0.80
HbA_{1c} evaluation within 3 months of fertility treatment or pregnancy	57.8	73.3	0.15
Median HbA_{1c} level (interquartile range) within 3 months of fertility treatment or pregnancy	7.0 (6.2–8.1)	6.7 (6.3–8.9)	0.88
Good glycemic control ($HbA_{1c} < 7.0\%$) within 3 months of fertility treatment or pregnancy	31.3	40.0	0.45

Data are percentages unless otherwise indicated.

women in the control group had slightly better glycemic control parameters compared with women in the fertility group, although none reached statistical significance.

As for use of potentially hazardous drugs (i.e., statins, ACE inhibitors, or ARBs), 11 women in the control group (37%) filled at least one prescription in the year before pregnancy, and 3 women in this group filled at least one prescription in the month after pregnancy diagnosis. Among women undergoing fertility treatments, 34 women took potentially hazardous drugs within 1 year of fertility treatment (41%), and 12 women in 16 fertility cycles filled at least one prescription in the month after fertility treatment.

Next, we wanted to evaluate maternal characteristics that might influence folic acid use and glycemic control among women who undergo fertility treatments. As summarized in Table 2, folic acid use and median HbA_{1c} level were better among Jews and in women who received fertility treatment other than clomiphene citrate. In binary multivariate logistic regression analysis (after controlling for marital status, maternal age, number of children, ethnicity, number of fertility cycles, and type of fertility cycle), the odds ratios for any folic acid use were 2.25 among Jews (95% CI 1.29–3.94) and 1.87 in women who received fertility treatment other than clomiphene citrate (1.05–3.33). Table 2 also shows that the median HbA_{1c} level was better in women who received fertility treatment other than clomiphene citrate and among Jews. However, in binary multivariate logistic regression analysis (after controlling for all of the above variables), the only significant parameter associated with good diabetic control (i.e., HbA_{1c} <7% within 3 months of fertility cycle) was fertility treatment other than clomiphene citrate (odds ratio 2.16 [1.17–3.98]). There were no significant factors that influenced the rate of HbA_{1c} evaluation within 3 months of fertility treatment (Table 2).

CONCLUSIONS—To the best of our knowledge, this is the first study to evaluate the periconception medical care of diabetic women who undergo fertility treatment. It might be assumed that after a long period of living in preparation for a possible pregnancy, patients undergoing fertility treatment would be ideally prepared for pregnancy; however, this is not the case. We found that many women underwent fertility treatment despite poor glycemic control, only a small fraction used folic acid regularly and too many continued the use of potentially harmful medications during the first trimester of pregnancy. Moreover, diabetic women who used assisted reproduction techniques were not better prepared for pregnancy compared with diabetic women with spontaneous pregnancy.

There are many studies in the general population on folic acid intake before pregnancy. For example, the Morbidity and Mortality Monthly Report of the Centers for Disease Control and Prevention (13) shows that in 2007, 40% of women of childbearing age in the U.S. reported taking vitamin supplements containing folic acid. However, there are only scant data about the use of folic acid before the (planned) pregnancies of patients with fertility problems. Two small studies from the U.S. (14) and Hungary (15) reveal that preconception folic acid use was higher among infertile women compared with control subjects (~53 vs. 30%). In contrast, a large German study of pregnant women after intracytoplasmic sperm injection shows that only 38.1% of subjects took folic acid in the preconception period (16). Furthermore, Nilsen et al. (17), in a large survey from Norway, found that overall, only 10.2% of women used folic acid supplements in the periconception period. Folic acid use was somewhat higher among women undergoing in vitro fertilization treatment (24.9%) and among women with diabetes (17.3%).

Preconception folic acid intake is not much better among diabetic patients, although their risk for a child with neural tube defect is much higher. A study from the Netherlands (18) among pregnant

Table 2—*Quality measure of preconception care in women undergoing fertility treatment*

Maternal characteristic	*n*	At least one folic acid prescription filling in 3 months	*P* value	HbA_{1c} evaluation within 3 months	*P* value	Median HbA_{1c} level (interquartile range)	*P* value
Maternal age							
<35 Years	92	51.1	0.19	65.2	0.09	6.9 (6.2–7.9)	0.44
>35 Years	138	41.3		52.9		7.1 (6.3–8.1)	
Marital status							
Yes	195	46.2	0.63	63.2	0.08	7.0 (6.3–7.9)	0.77
No	35	40.0		45.7		7.5 (6.2–8.3)	
Ethnicity							
Jew	128	55.4	**<0.001**	60.2	0.50	6.9 (6.0–7.9)	0.056
Non-Jew	102	32.4		54.9		7.0 (6.4–8.4)	
Children							
None	102	43.1	0.66	56.9	0.90	7.1 (6.5–8.6)	0.26
1 Or more	128	46.9		58.6		6.9 (6.2–7.9)	
Fertility treatment type							
Clomiphene	88	32.9	**0.005**	56.8	0.91	7.3 (6.6–9.0)	**<0.001**
Other	142	52.8		58.5		6.7 (6.0–7.8)	
Number of fertility cycles							
1–2	132	42.4	0.39	52.3	0.06	6.9 (6.3–8.3)	0.89
3 Or more	98	50.0		65.3		7.0 (6.2–7.9)	

Data are percentages unless otherwise indicated. Significant data are indicated in boldface.

type 1 diabetic women confirms a relatively high preconception folic acid intake of 70%. In contrast, a large survey from the U.K. (11) shows that only 27% of diabetic patients used folic acid before pregnancy. Furthermore, in a population-based study in the north of England (19), only 45% of diabetic patients took folic acid in the preconception period. In addition, the study demonstrates that among diabetic women who received preconception counseling (40.8%), prepregnancy folic acid use was significantly higher at 68.4% compared with only 31.6% in diabetic pregnant women who did not receive preconception care (19).

Our findings are in agreement with the above results; we found that only one-quarter of diabetic patients in both groups took folic acid supplementation regularly during the fertility treatments and prior to pregnancy to better prepare themselves for pregnancy. Our findings are also in agreement with prior findings on folic acid use in Israel. In a survey conducted by the Public Health Service, 1,860 pregnant and postpartum women in Israel were interviewed. Of these women, 34% stated that they used folic acid in the preconception period (20). Thus, despite the great effort required from women who undergo fertility treatment, simple measures, such as daily periconception folic acid intake, that can improve pregnancy outcome are still rarely used.

Good glycemic control prior to and in the beginning of pregnancy is crucial to reduce the rate of congenital malformations and spontaneous abortions among diabetic patients (1–5,19). Nonetheless, many studies demonstrate that most diabetic patients get pregnant despite poor diabetic control. In a French multicenter survey of women with pregestational diabetes, approximately one-quarter had an HbA_{1c} >8.0% in the first trimester, and this was associated with increased risk for adverse perinatal outcome (8). A large Danish study (10) among type 1 diabetic patients shows that only 30.4% had an HbA_{1c} <6.9% in the periconception period, and these women had lower risk for serious adverse perinatal outcome. In a similar manner, a large survey from the U.K. (2) illustrates that 68% of subjects had a recorded measurement of HbA_{1c} in the first trimester; yet, only 37% had good glycemic control defined by HbA_{1c} <7%. Again, suboptimal glycemic control before and during pregnancy was associated with poor pregnancy outcome. Furthermore, in a population-based study in the north of England (19), only 53% of diabetic patients had a preconception HbA_{1c} record, and of those with records, 74% had suboptimal glycemic control with an HbA_{1c} >7.0%. The researchers also found that diabetic women who received preconception counseling (40.8%) had a significantly higher rate of good glycemic control prior to pregnancy (63.8%) compared with only 36.3% in diabetic pregnant women who did not receive preconception care (19).

Thus, spontaneous pregnancies in women with diabetes are still poorly planned. One would expect better preparation in women who undergo fertility treatments; however, in a thorough literature search, we could not find any articles that dealt with this issue directly. Our study demonstrates that although infertile diabetic women are under medical supervision, preconception counseling regarding the importance of diabetes control is lacking. Less than two-thirds had an HbA_{1c} recording within 3 months of fertility treatment, and only one-third of these had evidence of good glycemic control with an HbA_{1c} <7.0%. Even more disappointing was the finding that diabetic women undergoing fertility treatments had no better glycemic control compared with diabetic women with spontaneous pregnancy.

Drug use in the preconception period and early pregnancy is very common, including drugs that are teratogenic or potentially hazardous. A study from the U.S. (21) confirms that ~4.5% of U.S. pregnancies are exposed to potentially teratogenic class D or X medications after the initial prenatal care visit. In a similar manner, a large study from the U.K. (22) shows that category X medications, with potential teratogenic risk that outweighs maternal benefit, were prescribed to 7% of women in the preconception period and to 0.6% of women during early pregnancy. Furthermore, a large retrospective study from Finland (23) shows that 3.4% of pregnant women purchased at least one drug classified as clearly harmful during pregnancy. However, very little is known about medication during pregnancy after assisted reproduction. Ludwig et al. (16), in a large study on pregnant women after intracytoplasmic sperm injection, found that almost 85% of women took some medication, other than iron or vitamins, during pregnancy, and two-thirds took more than one medication. However, these researchers did not comment on the use of potentially harmful drugs. In a literature review, we could not find any other articles that dealt with the use of potentially teratogenic drugs in either infertile women or in pregnant diabetic women. Our results demonstrate that similar to the general pregnant population, too many diabetic women continue the use of potentially harmful drugs in the beginning of pregnancy and after fertility treatment. This finding is particularly worrisome in diabetic patients who undergo fertility treatments and, thus, had ample opportunities for proper preconception advice and recommendation to discontinue the use of such medications prior to pregnancy.

Another important finding in the current study was that folic acid intake and glycemic control were somewhat better among Jewish compared with non-Jewish infertile women. Disparities in diabetes care, especially among low socioeconomic patients and those who belong to an ethnic minority, have been documented over the years. For example, a population-based study in the north of England (19) shows that diabetic women of white British ethnicity and those of higher socioeconomic status were more likely to receive preconception counseling. In a similar manner, a recent study from Israel (24) illustrates that low socioeconomic status and belonging to an ethnic minority are associated with less favorable diabetes care and control. Unfortunately, we do not have data on socioeconomic status or education in our study. Nonetheless, culturally appropriate diabetes care and education is needed to improve diabetes care and ensure better pregnancy outcomes in all population groups.

There are several limitations to our work. We do not have data on the success rate of the various fertility treatments, nor do we have data on pregnancy outcome or complications. Thus, we cannot assess the correlation between proper preconception care (i.e., folic acid use and good glycemic control) and pregnancy outcome; however, this was not the aim of this study. Also, our work was not powered enough to demonstrate small differences in quality measures between the two groups. Yet in most aspects, women in the fertility group did not have better preconception care compared with women in the spontaneous pregnancy group (Table 1). Thus, it is highly unlikely that a much larger study would find that, indeed, women with fertility problems received significantly better care.

We calculated folic acid use based on prescription fillings in CHS pharmacies. It is possible that some women purchased folic acid or other multivitamins including folic acid as over-the-counter drugs in other pharmacies. However, since these women purchased the fertility drugs in CHS pharmacies and the cost of the vitamins is similar in all pharmacies, it is unlikely that this would change substantially our calculations of folic acid use. Moreover, most studies on folic acid use (11,13–20) are based on questionnaires or interviews of pregnant or postpartum women. Thus, while our study might have underestimated preconception folic acid use, women's self-report on preconception daily folic acid use is probably overreported. To the best of our knowledge, there is no study that evaluates preconception folic acid intake by pill counting, which is more accurate.

Diabetic patients were identified based on HbA_{1c} recordings or filling of an antidiabetic drug prescription. It is possible that we did not identify a small number of diabetic patients, for example, those who have very good diabetic control and treatment with diet only. Also, women with undiagnosed diabetes and, thus, no HbA_{1c} tests or antidiabetic treatment were not accounted for. Still, we believe that we identified most women with type 1 or type 2 diabetes, and the few unidentified patients that belong to both groups could not significantly change our findings. Metformin is sometimes used in nondiabetic infertile women with polycystic ovary syndrome. Because of the retrospective study design, we could not ascertain the indication for metformin treatment. Thus, women who used metformin but no other antidiabetic drug were not categorized as having diabetes, since it might skew the results (i.e., there is no indication for HbA_{1c} evaluation in polycystic ovary syndrome patients taking metformin).

As for potentially teratogenic drugs, we chose to examine the use of only those drugs that are commonly used by diabetic women and for which there is a firm recommendation to stop using before conception. One might argue that a woman can fill a prescription and still not use the medication; thus, prospective evaluation of harmful medication use might be lower than what we reported. However, these women should have received guidance to stop using these drugs prior to conception and, thus, should not have filled prescriptions for potentially teratogenic drugs in the month after fertility treatment when they might be pregnant. Use of potentially harmful medications in early pregnancy should be negligible, especially among women who undergo fertility treatment.

In conclusion, we found that the medical care of diabetic women who undergo fertility treatment is suboptimal and needs improvement. Moreover, diabetic women who used assisted reproduction techniques were not better prepared for pregnancy compared with diabetic women with spontaneous pregnancy. Preconception care and counseling is a form of primary prevention that includes three components: risk assessment, health promotion, and intervention to improve pregnancy outcome. Couples who are referred to an infertility unit invest a lot of effort into conceiving. These women are highly motivated in their desire to achieve a pregnancy and, thus, represent an ideal group for preconception care. Therefore, it is astonishing that less than one-quarter of these patients prepared themselves for pregnancy by taking folic acid regularly and only one-third had good glycemic control prior to fertility treatment. Considering the great effort that is needed to achieve these pregnancies, the suboptimal preconception care is surprising and worrisome. Couples who are referred to an infertility clinic usually undergo a thorough fertility workup before treatment, yet no standardized medical evaluation exists. A recent review article suggests that every woman who is a candidate for fertility treatment should undergo a structured pretreatment medical assessment (25). This assessment should include a thorough medical questionnaire with special attention to risk factors, chronic medical disease, medications, and family history. Before starting fertility treatment, appropriate treatment of all medical conditions, optimization of disease control, and cessation of potentially teratogenic medications can improve women's health status and reduce pregnancy-related complications. We believe that these guidelines are especially important for women with diabetes. Also, more intensive and targeted counseling is needed to optimize care in infertile diabetic patients. It is probable that a multidisciplinary team approach is needed, with a specialized clinic that can give optimal preconception evaluation and care for diabetic patients prior to and in parallel with the fertility treatment in the infertility units.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

S.R.-M. designed the study, collected and analyzed data, and wrote the manuscript. R.A. contributed to discussion and reviewed and edited the manuscript.

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