



Association of Implementation of a Comprehensive Preconception-to-Pregnancy Management Plan With Pregnancy Outcomes Among Chinese Pregnant Women With Type 1 Diabetes: The CARNATION Study

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OBJECTIVE

To investigate the effect on pregnancy outcome of integrating a comprehensive management plan for patients with type 1 diabetes (T1D) into the World Health Organization universal maternal care infrastructure.

RESEARCH DESIGN AND METHODS

A comprehensive preconception-to-pregnancy management plan for women with T1D was implemented in 11 centers from 8 Chinese cities from 2015 to 2017. Sequential eligible pregnant women ($n = 133$ out of 137 initially enrolled) with T1D and singleton pregnancies attending these management centers formed the prospective cohort. The main outcome was severe adverse pregnancy outcome comprising maternal mortality, neonatal death, congenital malformations, miscarriage in the second trimester, and stillbirth. We compared pregnancy outcomes in this prospective cohort with two control groups with the same inclusion and exclusion criteria: a retrospective cohort ($n = 153$) of all eligible pregnant women with T1D attending the same management centers from 2012 to 2014 and a comparison cohort ($n = 116$) of all eligible pregnant women with T1D receiving routine care from 2015 to 2017 in 11 different centers from 7 cities.

RESULTS

The rate of severe adverse pregnancy outcome was lower in the prospective cohort (6.02%) than in either the retrospective cohort (18.30%; adjusted odds ratio [aOR] 0.31 [95% CI 0.13–0.74]) or the contemporaneous comparison cohort (25.00%; aOR 0.22 [95% CI 0.09–0.52]).

CONCLUSIONS

The substantial improvements in the prospective cohort are evidence of a potentially clinically important effect of the comprehensive management plan on pregnancy outcomes among Chinese pregnant women with pregestational T1D. This supports the development of similar approaches in other countries.

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Women with type 1 diabetes (T1D) are at increased risk of adverse pregnancy outcomes (1). Better glycemic control achieved via technologies such as continuous glycemic monitoring (CGM), preconception folic acid supplementation, and weight-gain management improve pregnancy outcomes in women with T1D (1,2). Comprehensive maternal care management guidelines for pregnancy complicated with T1D have been implemented in Europe (3,4) with an associated decline in stillbirth and congenital malformation rates (1,5), but pregnancy outcomes in patients with T1D remain suboptimal (6–8). In some high-income countries, no improvement in certain adverse outcomes was observed in the past decade (7,8). Many pregnant women with T1D live in low- or middle-income countries that lack the necessary social and medical resources required to implement comprehensive maternal management guidelines during pregnancy (9,10), and the effectiveness of guidelines appropriate for implementation in low- or middle-income countries is unknown. Such evidence is needed as a basis for effective and practicable guidance in developing countries.

The World Health Organization (WHO) has recommended a universal maternal care framework that has been successfully implemented globally, including in China and many low- and middle-income countries (11,12). Previous studies also supported that that integration of disease-specific maternity services into that preexisting framework of the general maternal care can be beneficial for the pregnant women complicated with chronic conditions (13,14). Therefore, the integration of a comprehensive management plan for women with T1D who are planning a pregnancy or are pregnant into the preexisting WHO maternal care infrastructure in China offered a unique opportunity to investigate the effectiveness of such an intervention in a middle-income country. This study, the CARNATION study, was conceived to gather such evidence.

RESEARCH DESIGN AND METHODS

Development of the Comprehensive Pregnancy Management Plan for Women With T1D

In 2014, the National Health and Family Planning Commission of China initiated a project aimed to improve the pregnancy

care for women with T1D. A group of experts (the CARNATION committee) reviewed published articles in peer-reviewed journals, consensus statements, and international guidelines (15–18) and proposed a comprehensive, evidence-based preconception-to-pregnancy management plan for women with T1D. The content of the management plan was then adapted to be embedded into the preexisting Chinese national maternal care framework to facilitate implementation.

The management plan is made up of a checklist for the relevant health care providers (HCPs), a one-page educational leaflet for pregnant women with T1D and their families, and educational support for both the patients and the HCPs. The checklist for the HCPs focused on 20 items of care, which covered different stages of care: preconception care, pregnancy care during each trimester, and postpartum care. The items included information on multidisciplinary cooperation and recommendations on diet, management of diabetes and its complications, blood pressure management, prevention and treatment of preeclampsia, and other medical issues (Supplementary Table 1). The one-page educational leaflet for pregnant women with T1D and their families gave specific information on glycemic targets, dietary advice, and important symptoms for identifying potential complications (Supplementary Table 2).

The management plan was approved by the National Health and Family Planning Commission of China. Since 2015, the plan was pilot tested in 11 general medical centers from 8 cities across China (Supplementary Table 3). These centers were selected from member institutions of the Chinese Diabetes Society. They were all public hospitals, had the capability to care for high-risk pregnancies, such as pregnancy in diabetes, and were geographically evenly distributed. At all of these management centers, the management plan was embedded into the preexisting universal Chinese maternal care infrastructure guidelines, which were developed based on recommendations by the WHO (routine antenatal care) (19) (Fig. 1). Briefly, the checklist and the one-page leaflet were distributed to HCPs and women with T1D who were pregnant or planning pregnancy in obstetric/endocrinology clinics at all management centers. The CARNATION committee organized a 2-day workshop to provide

educational support for the personnel involved in the delivery of the management plan (Supplementary Material, Management of Care Integration), with written care plans for implementation. The committee also released educational materials via national academic meetings, professional websites, and social media.

Apart from the educational one-page leaflet, patient education for women with T1D attending the management centers was also given by free online materials released by the CARNATION committee, via a smartphone-based application (20). This application was introduced to women with T1D by their care providers.

Prospective Cohort

Between 1 January 2015 and 31 December 2017, we prospectively and consecutively collected data of all of the pregnant women with pregestational T1D treated in the 11 centers where the comprehensive management plan for T1D was implemented. For analysis, we included those women with pregestational T1D: 1) who had a singleton pregnancy, and 2) who had a live birth or stillbirth or miscarriage during the study period. We excluded those: 1) who had multiple pregnancies, and 2) who had a termination of pregnancy for nonmedical reasons. These pregnant women with T1D in the management centers comprised the prospective cohort. Details of data collection are available in the Supplementary Material. Written informed consent was obtained from each of these women. From 2015 to 2017, among 169,752 pregnancies in these management centers, 137 pregnant women with pregestational T1D were initially enrolled. Two were subsequently found to have multiple pregnancies on ultrasonic examination, and another two elected for pregnancy termination due to nonmedical reasons. All 4 were excluded from the analysis, leaving 133 eligible participants (Fig. 2).

Control Groups

We compared pregnancy outcomes in the prospective cohort with two control groups. The first group is a retrospective cohort of all of the pregnant women with pregestational T1D who received antenatal care preceding the implementation of the management plan for T1D from 2012 to 2014 in the same 11 management centers as the prospective cohort and who fulfilled the same eligibility criteria

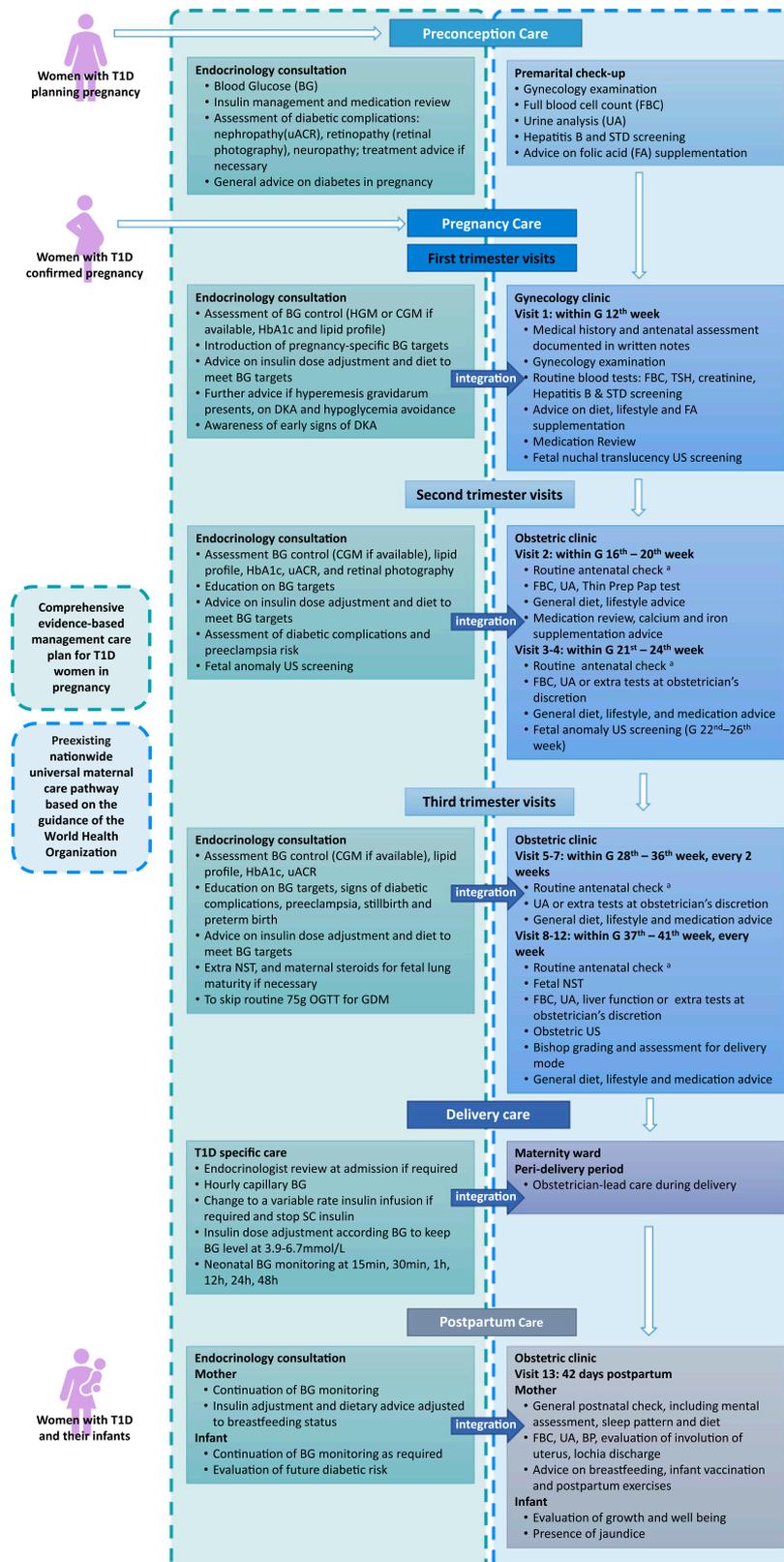


Figure 1—Integration of the comprehensive preconception-to-pregnancy management plan for T1D to the universal maternal care framework. This figure depicts the integration of the comprehensive evidenced-based preconception-to-pregnancy management plan for women with T1D into the mandatory visits of the Chinese nationwide universal maternal care pathway based on the guidance of the WHO. A routine antenatal check includes measurement of maternal height, weight, blood pressure, uterus fundal height, and abdominal circumference, assessment of edema, and measurement of fetal heart rate. BP, blood pressure; DKA, diabetic ketoacidosis; FA, folic acid; FBC, full blood cell count; G, gestational; HGM, home blood glucose monitoring; NST, nonstress test; OGTT, oral glucose tolerance test; STD, sexually transmitted disease; TSH, thyroid-stimulating hormone; uACR, urinary albumin-to-creatinine ratio; US, ultrasound.

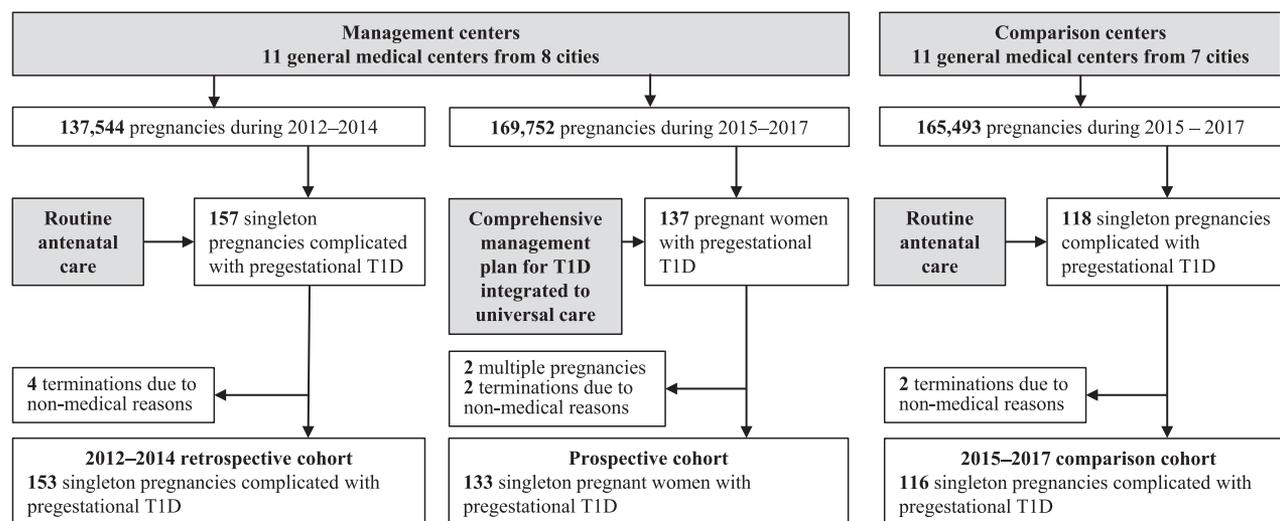


Figure 2—Flowchart of inclusion and exclusion of the participants.

as for the prospective group. These constituted 153 eligible pregnant women with T1D out of the >137,544 pregnancies who received routine antenatal care from 2012 to 2014 at the management centers, preceding the implementation of the management plan (Fig. 2).

The second group is a comparison cohort of eligible pregnant women with pregestational T1D who received routine antenatal care without the comprehensive management plan in 11 different centers during the study period of 2015–2017. In these comparison centers, the same national maternal care infrastructure as the management centers was applied, but not the management plan for T1D. We selected these comparison centers from seven cities across China (Supplementary Table 4). They were also public hospitals, in cities with similar demographic and economic characteristics, and had similar numbers of annual births and medical facilities as the management centers. We applied the same eligibility criteria to the comparison cohort in the analysis. There was a total of 116 eligible pregnancies with T1D out of 165,493 pregnancies receiving routine care from 2015 to 2017 at the comparison centers, all of whom were included in the analysis (Fig. 2).

Data of eligible pregnancies from the two control groups were compiled from medical records by trained staff. All data were anonymized and reviewed by a trained investigator in the study group (see Supplementary Material, Data collection).

Outcome Measurements

The main outcome was severe adverse pregnancy outcome, which was a composite of maternal mortality, neonatal death, congenital malformations, miscarriage in the second trimester, and stillbirth.

Maternal mortality, neonatal death, and congenital malformations were defined according to a previous report (21) (Supplementary Table 5). Miscarriage in the second trimester and stillbirth were defined as any pregnancy loss or the delivery of a fetus showing no signs of life after the 12th gestational week. The CARNATION committee chose to focus on these miscarriages and stillbirths because these outcomes are unambiguous and uniformly documented in the pregnancy notes and hospital information system throughout 2012 to 2017 at all participating centers.

Other outcomes of interest included: cesarean section (CS), gestational age at birth, preterm birth, birth weight, and other neonatal complications including neonatal hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, and admission to the neonatal intensive care unit (NICU) (21) (Supplementary Table 5).

Preconception diabetes care was assessed by: 1) rates of women having preconception and/or the first trimester hemoglobin A_{1c} (HbA_{1c}) tests, and 2) rates of women on appropriate insulin regimens as recommended by the management plan during the preconception period and/or the first trimester. We defined appropriate insulin regimens as the insulin

regimens recommended by the guidelines (17,18,22), including basal-bolus insulin regimens using multiple daily injections or insulin pump. Previous studies showed that many Chinese patients with T1D used self-mixed insulin or twice-daily premixed insulin (23,24), which proved less effective (25). Therefore, we considered using or changing to the appropriate insulin regimen as part of preconception care.

Statistical Analysis

According to a previous report (26) and open data from the local statistics bureaus, pregnancies complicated with T1D account for ~0.1% of total deliveries. The incidence of a composite outcome of maternal death, neonatal death, and neonatal congenital malformation was 20% in women with T1D. To achieve 90% power at a two-sided 5% significant level, we planned a sample size of 110,000 deliveries and 110 women with pregestational T1D in the prospective cohort study. The comparison between the prospective cohort and each of the comparison population was designed as 1:1 matched case-control study. The incidence of the primary outcome composite of maternal mortality, neonatal death, congenital malformations, miscarriage in the second trimester, and stillbirth was 21.7% in women with T1D in our previous study (26). The incidence of composite adverse pregnancy outcomes in women with T1D could reduce to ~6% based on other studies (3). We estimated that a sample size of 114 women with pregestational T1D in a matched case-control study would

achieve 90% power at a two-sided 5% significant level.

Comparisons were made of differences in maternal characteristics and pregnancy outcomes in the prospective cohort with each of the two comparison populations using Pearson χ^2 test, Fisher exact method, or Student *t* test where appropriate.

Logistic regression analysis was performed to estimate the odds ratios of adverse pregnancy outcomes in the prospective cohort compared with each of the control groups. We adjusted for maternal age at conception, duration of diabetes at conception, preconceptional diabetic complications, and education level. We did not include alcohol consumption or smoking because the prevalence of these among Chinese pregnant women is extremely low (27,28). Analyses were performed using Stata Version.14.0 and IBM SPSS Version.23.0.

Ethics

This study has been approved by the ethics committee of each participating center. These committees agreed that individual patient consent was waived for using anonymized data in the control groups.

RESULTS

Table 1 shows the maternal characteristics of the three cohorts. Overall, the average age at conception was 28.51 ± 4.14 years, with an average duration of diabetes of 6.88 ± 5.65 years in all participants. Except for slight differences in age at diabetes diagnosis and diabetes duration, no significant difference was observed in the preconceptional maternal characteristics between those in the prospective cohort and the comparison populations. For the participation of preconception diabetes care, in the prospective cohort, rates of preconception HbA_{1c} testing and appropriate insulin regimen use were 78.19% and 90.23%, respectively. These rates were significantly higher compared with those either in the 2015–2017 comparison cohort (50.00% and 56.90%, respectively) or those in the 2012–2014 retrospective cohort (20.26% and 61.44%, respectively).

Table 2 summarizes the pregnancy outcomes of the three cohorts. The rate of severe adverse pregnancy outcome in the prospective cohort (6.02%) was lower than the 2015–2017 comparison cohort (25.00%; $P < 0.001$) and the 2012–2014 retrospective

cohort (18.30%; $P = 0.002$). A decline in the rate of miscarriage in the second trimester and stillbirth was observed in the prospective cohort (1.50%) compared with both the 2015–2017 comparison cohort (20.69%; $P < 0.001$) and the 2012–2014 retrospective cohort (9.80%; $P < 0.001$). Details of causes of the miscarriage in the second trimester and stillbirth are available in Supplementary Table 6.

The prospective cohort had lower rates of CSs (63.28%), preeclampsia (5.26%), and large-for-gestational age babies (LGA; 14.62%) compared with both the 2015–2017 comparison cohort (CS 81.1%, $P = 0.004$; preeclampsia 27.59%, $P < 0.001$; and LGA 25.29%, $P = 0.049$) and the 2012–2014 retrospective cohort (CS 78.79%, $P = 0.006$; pre-eclampsia 15.03%, $P = 0.007$; and LGA 32.31%, $P = 0.001$), respectively.

In the logistic regression models, after adjustment for potential confounding variables, the implementation of the comprehensive management plan for T1D was significantly associated with lower odds of severe adverse pregnancy outcome in the prospective cohort, with 78% lower odds comparing the prospective cohort with the 2015–2017 comparison cohort (adjusted odds ratio 0.22 [95% CI 0.09–0.52]; $P = 0.001$) and 69% lower odds comparing the prospective cohort with the 2012–2014 retrospective cohort (adjusted odds ratio 0.31 [95% CI 0.13–0.74]; $P = 0.009$). Similarly, significantly lower odds were also observed for miscarriage in the second trimester and stillbirth and admission to NICU in the prospective cohort (Supplementary Table 7).

CONCLUSIONS

The main finding of this study is that the implementation of this comprehensive management plan was associated with a significantly and substantially lower risk of the severe adverse pregnancy outcome and several other adverse outcomes among pregnant women with T1D, under a relatively low-resource setting.

This has major clinical implications. Many low- and middle-income countries with relatively limited health care resource have achieved significant improvement in pregnancy outcomes among the general population (29). This improvement follows the implementation of the maternal care recommended by the WHO. Such improvement following the national implementation of the WHO framework could

also be observed in China: maternal and neonatal mortality in the general population has decreased significantly over the past 25 years (12). However, an excess of adverse pregnancy outcomes still occurred for Chinese women with T1D from 2004 to 2014 (26), despite the improvement among the general population. The subsequent improvement in pregnancy outcomes following the implementation of the comprehensive management plan for T1D described in this study could be attributed to several factors.

First, guidance for multiple aspects of differential pregnancy care for T1D is incorporated into our comprehensive management plan. Previous evidence shows that single interventions can improve certain pregnancy outcomes, but may not be enough in themselves to significantly improve the whole range of adverse pregnancy outcomes seen in women with T1D. For example, the ATLANTIC-DIP studies (3) showed that the rates of stillbirth and congenital malformations over a 10-year period were reduced following an increased uptake in preconception care from 28% to 52%. Better control of maternal hyperglycemia is known to lower the risk of fetal and neonatal complications, including neonatal congenital malformations, LGA, macrosomia, preterm birth, miscarriage, and stillbirth (5,30,31). Limiting pregnancy maternal weight gain also lowers the risk of LGA and preterm birth (1). Good blood pressure control throughout the peripregnancy period reduces the risk of preeclampsia (1). Our management plan provided recommendations on multiple aspects of T1D pregnancy care including preconception care, discontinuation of teratogenic medications, the constant emphasis on diet, glycemic targets, insulin regimen adjustments, blood pressure control, and pregnancy weight gain (Supplementary Tables 1 and 2). Our findings supported that, when all of these separate evidence-based strategies are amalgamated into one comprehensive T1D management plan embedded into the country's universal maternal care package, overall adverse pregnancy outcomes declined.

Second, the integration of the T1D management plan to the country's universal maternal care framework enhanced the uptake of the management, despite relatively limited health care resource. Improvement in the uptake of specialized care for women with T1D is a

Table 1—Maternal characteristics of the studied women with T1D

	Prospective cohort (2015–2017)	Retrospective cohort (2012–2014)	Comparison cohort (2015–2017)	Prospective vs. retrospective P value	Prospective vs. comparison P value
Number of pregnant women	133	153	116	NA	NA
Age at conception, years, mean (SD)	28.8 (3.9)	28.3 (4.0)	28.4 (4.6)	0.273	0.467
Age at diagnosis, years, mean (SD)	20.5 (6.9)	22.6 (6.8)	23.0 (6.8)	0.010	0.005
Duration of diabetes, years, mean (SD)	8.5 (6.4)	6.3 (5.3)	5.8 (4.7)	0.002	<0.001
Preconception/1st trimester HbA _{1c} %, mean (SD)	7.0 (1.3)	7.6 (2.2)	7.0 (1.9)	—	—
mmol/mol, mean (SD)	53 (14)	60 (24)	53 (21)	0.137	0.892
n/N (%)	104/133 (78.19)	31/153 (20.26)	58/116 (50.00)	<0.001	<0.001
HbA _{1c} ≤6.5% or 48 mmol/mol, % (n/N)	45.2 (47/104)	38.7 (12/31)	51.7 (29/58)	0.523*	0.425*
HbA _{1c} at delivery %, mean (SD)	6.1 (0.75)	6.8 (1.53)	7.0 (2.01)	<0.001	0.003
mmol/mol, mean (SD)	43 (8)	50 (17)	53 (22)	<0.001	0.003
n/N (%)	86/133 (64.6)	78/153 (51.0)	56/116 (48.3)	0.020	0.009
HbA _{1c} ≤6.5% or 48 mmol/mol, % (n/N)	79.1 (68/86)	52.6 (41/78)	55.4 (31/56)	<0.001*	0.003*
Preconception/1st trimester insulin regimen	—	—	—	—	—
Insulin pump, n (%)	52 (39.1)	21 (13.7)	14 (12.1)	<0.001	<0.001
MDI, n (%)	68 (51.1)	73 (47.7)	52 (44.8)	0.564	0.321
Others,† n (%)	13 (9.8)	59 (38.6)	50 (43.1)	<0.001	<0.001
Preconceptional diabetes complications, n (%)	11 (8.7)	21 (13.7)	12 (10.3)	0.144	0.573
Preconceptional blood pressure, n	87	45	115	NA	NA
SBP, mmHg, mean (SD)	111.0 (11.1)	116.6 (14.6)	123.9 (18.8)	0.025	<0.001
DBP, mmHg, mean (SD)	71.0 (8.6)	74.0 (12.2)	80.1 (13.7)	0.141	<0.001
Blood pressure at 33–36 weeks, n	111	150	115	NA	NA
SBP, mmHg, mean (SD)	112.5 (12.7)	123.0 (17.5)	124.3 (18.7)	<0.001	<0.001
DBP, mmHg, mean (SD)	70.6 (8.4)	76.0 (11.6)	80.6 (14.0)	<0.001	<0.001
Preconception body weight, kg, mean (SD)	55.0 (7.9)	NA	NA	NA	NA
Body weight at delivery, kg, mean (SD)	67.8 (7.7)	NA	NA	NA	NA
Body weight gain, kg, mean (SD)	12.2 (5.1)	NA	NA	NA	NA
Current smoker, n	0	0	2	NA	NA
Current alcohol consumer, n	0	0	1	NA	NA
Middle school or higher, n (%)	131 (98.5)	93 (95.9)	73 (97.3)	0.243	0.558
Participation in preconception management,‡ n (%)	98 (73.7)	24 (15.7)	41 (35.3)	<0.001	<0.001

DBP, diastolic blood pressure; MDI, multiple daily injections of basal-bolus insulin; NA, not applicable; SBP, systolic blood pressure. *These comparisons were performed among the patients whose HbA_{1c} values were available. †Other insulin regimens included multiple injections of premixed insulin/insulin analogs, multiple injections of short-acting or rapid-acting insulin, single dose of basal insulin, or other insulin regimens that were not recommended by guidelines for the treatment of pregnant women with T1D. ‡Participation in preconception management was defined as the proportion of women who had tested HbA_{1c} and using/ changing to insulin regimen as guidelines recommended during the preconception period or the first trimester of pregnancy.

Table 2—Pregnancy outcomes of the studied women with T1D

	Prospective cohort (2012–2014)		Retrospective cohort (2012–2014)		Comparison cohort (2015–2017)		Prospective vs. retrospective P value		Prospective vs. comparison P value	
	n	(%)	n	(%)	n	(%)				
Number of pregnant women	133		153		116		NA		NA	
Severe adverse pregnancy outcome,* n (%)	8 (6.0)		28 (18.3)		29 (25.0)		0.002		<0.001	
Maternal death, n (%)	0 (0)		1 (0.65)		0 (0)		NA		NA	
CS, n (%)	81 (63.3)		104 (78.8)		73 (81.1)		0.006		0.004	
Preeclampsia, n (%)	7 (5.26)		23 (15.03)		32 (27.59)		0.007		<0.001	
Miscarriage in the 2nd trimester and stillbirth, n (%)	2 (1.5)		15 (9.8)		24 (20.7)		<0.001		<0.001	
Number of live births	130		132		91		NA		NA	
Neonatal death, n (%)	0 (0)		6 (4.6)		1 (0.9)		NA		NA	
Congenital heart malformation, n	0		5		0		NA		NA	
Neonatal respiratory distress syndrome, n	0		1		0		NA		NA	
Unknown cause, n	0		0		1		NA		NA	
Congenital malformation, n (%)	6 (4.6)		11 (8.3)		4 (4.4)		0.222		1	
Heart malformation, n	5		7		4		NA		NA	
Polydactyly, n	1		4		0		NA		NA	
Cerebral malformation, n	0		1		0		NA		NA	
Preterm birth, n (%)	18 (13.9)		23 (17.4)		27 (29.7)		0.425		0.006	
Early preterm birth (24–30 weeks), n (%)	3 (2.3)		5 (3.8)		6 (6.6)		0.752		0.224	
Gestational age at delivery, weeks, mean (SD)	38.5 (1.8)		37.5 (1.8)		36.7 (2.5)		<0.001		<0.001	
Birth weight# g, mean (SD)	3,296.0 (592.8)		3,373.2 (678.1)		3,063.9 (758.0)		0.329		0.750	
SGA, n (%)	8 (6.2)		8 (6.2)		10 (11.5)		1.000		0.162	
LGA, n (%)	19 (14.6)		42 (32.3)		22 (25.3)		0.001		0.049	
Macrosomia, n (%)	11 (8.5)		20 (15.2)		11 (12.6)		0.085		0.317	
Neonatal hypoglycemia, n (%)	20 (15.4)		21 (15.9)		10 (11.0)		0.907		0.348	
Neonatal jaundice, n (%)	33 (25.4)		29 (22.0)		24 (26.4)		0.516		0.869	
Respiratory distress, n (%)	6 (4.6)		7 (5.3)		9 (9.89)		0.798		0.174	
Admission to NICU, n (%)	37 (28.5)		55 (41.7)		40 (44.0)		0.025		0.017	

NA, not applicable; SGA, small-for-gestational age. *Severe adverse pregnancy outcome comprised maternal death, neonatal death, neonatal malformation, miscarriage in the second trimester, and stillbirth.
#The numbers of participants with data available were 130 for the prospective cohort, 130 for the retrospective cohort, and 87 for the comparison cohort.

challenge worldwide. Take the preconception care as an example: the participation rate worldwide for preconception care in women with T1D ranges from 35% to 71%, as measured by folate acid supplementation rate (3,32).

Likewise, in China, the public hospitals, including our participating centers, are the main HCPs and account for >90% of all hospital admissions (33). These hospitals are typically overcrowded with limited resources. However, by 2012, following collaboration between the public hospitals and government, a universal pregnancy care package became available for the entire Chinese population (12). With this in place, we were able to integrate our T1D management plan into the general framework with the printed checklists for HCPs and the one-page leaflet for women with T1D to follow at different stages of pregnancy. This integration meant that we were able to insert differential care for T1D in pregnancy into the mandatory universal antenatal visits easily, without extra personnel. Also, the one-page leaflet was well accepted by the pregnant women with T1D and mediated multidisciplinary cooperation: the participants would quickly understand when and where to seek assistance if a certain worrying sign occurred (Supplementary Table 2). As a result, the participation of preconception care measured by the rate of preconceptional HbA_{1c} measurement rose from 20.00% to 78.19% in the management centers providing the comprehensive T1D management plan compared with the 2015–2017 comparison centers that remained at 50.00%, highlighting the raise of uptake of preconception care. We must admit that some of the pregnancies in the prospective cohort were unplanned. These women missing preconception care had a higher rate of severe adverse pregnancy outcome (1 out of 10; 10.00%) compared with those who received preconception counseling (7 out of 123; 5.69%; $P = 0.582$), which was similar to that observed in both the retrospective and the comparison cohorts (Supplementary Table 8). Besides participation in preconception care, women with T1D in the management centers had better glycemic control as measured by the rate achieving glycemic target at delivery and had lower late trimester blood pressure measurements compared with the 2015–2017 comparison

cohort or the 2012–2014 retrospective cohort (Table 2). Moreover, results in the prospective cohort showed that 77.08% had a gestational weight gain within the Chinese guideline recommendations (22). Such improvements in multiple aspects of care could explain the decline in pregnancy loss, preeclampsia, preterm birth, neonatal congenital malformations, and LGA birth weight (1). These results suggest that the comprehensive management plan embedded within the preexisting universal pregnancy care framework is feasible and effective. Given that the components in the WHO recommended maternal care that China has adopted as routine antenatal care are universal and have achieved >90% coverage in developed areas and >50% in developing areas (29,34), our management plan could be generalized in other regions after adaption to the local maternal care framework. Potentially, our results may form the basis of changing the current clinical practice and health care policy for pregnancy care for women with T1D. Our findings strengthen the evidence for the integration of a specialized care package for women with manageable chronic diseases, such as T1D, into the preexisting maternal care framework to improve relevant pregnancy outcomes in relatively limited-resource settings.

Additionally, this study is the first to report both a decline in severe adverse pregnancy outcome as well as a decline in CS rates among women with T1D. The ATLANTIC-DIP studies reported an increase in CS rate from 49% (2005–2009) to 68% (2010–2014), despite a reduction in malformations and improved glycemic control following interventions (3). Although still higher than the CS rate among the general population (46.6%, median of 17 supercities in 2014) (35), the implementation of the management plan was followed by a 15% decline of CS among pregnant women with T1D. We hypothesize that the 2-day workshop of education for HCPs and the one-page educational leaflet resulted in an increased awareness of the benefits of vaginal birth. Also, the decreased incidence of LGA might have led to a reduction in CS rates.

A major strength of this study is the careful data collection through a large nationwide collaboration. Although the rate of pregnancy complicated with T1D

is low in China, through extensive collaborative efforts, we were able to ensure enough participants to observe a clinically meaningful improvement. The pilot testing of the management plan by the National Health and Family Planning Commission of China offered a unique opportunity for us to observe the effectiveness.

Moreover, we have adopted multiple controls to mitigate potential confounding factors. First, the management and control groups were all treated consistently within the structure of the Chinese national maternal care program, apart from the management plan, limiting the possibility that unrecognized variations in care between the groups contributed to the observed outcomes. Second, one control group was drawn from the same centers as the management group preceding the intervention, limiting the possibility of a contribution from geographic factors. Third, the second control group was contemporaneous with the managed prospective cohort, limiting the possibility that improvements of care over time within China could account for the improved outcomes. Finally, based on our results, we believe that unrecognized confounders are unlikely to have accounted for more than a minor part of the observed difference. First, the change in the main outcome measure is consistent with all of the several other predetermined outcomes of interest among the groups. Second, the two different control groups were consistent with one another. It thus appears likely that most, if not all, of the observed improvements are attributable to an effect of the management plan. The size of such an effect is substantial, with the decline in the main outcome of ~30% and 80% in the two control groups. But even so, pregnancy outcome in the management group was not as good as in the population without diabetes. This suggests that further refinements to the management plan should be evaluated. Nevertheless, the intervention had a highly favorable number needed to treat (number needed to treat was 8 when compared with the retrospective cohort and 6 when compared with the comparison cohort) to prevent an event of severe adverse pregnancy outcome, which was affordable and accepted by patients with T1D.

There are several limitations to the study. First, given the nature of the

observational study design and lack of randomization, we cannot eliminate all unmeasured confounding factors. But we limited impact of biased allocation among groups to the greatest extent by the enrollment of all of the eligible participants in the management centers and comparison centers during the designated period. Second, we did not include aspirin use in our management plan. This is because, when the project was launched, the evidence base for the use of aspirin to prevent preeclampsia in pregnant women with pregestational diabetes was not proven (22). Third, we recommended the use of CGM in our management plan, but the number of women using CGM in this study was limited due to economic constraints. We compared the glycemic control and pregnancy outcomes between the women in the prospective cohort who used CGM during pregnancy and those who did not. No significant difference was observed (Supplementary Table 9). Further improvements in pregnancy outcomes might have been achievable if more participants were able to use CGM, as evidenced by the CONCEPTT study (2).

The findings from this nationwide study suggest that for women with T1D, a comprehensive, preconception-to-pregnancy management plan integrated into the universal WHO maternal care framework is associated with a significantly lower rate of adverse pregnancy outcomes. The reduction of adverse outcomes may be attributable to multiple factors, including better uptake of preconception care, improved glycemic control, better blood pressure control, and limiting excessive gestational weight gain. The management plan achieved these improvements under a relatively resource-limited setting, suggesting that it was feasible and effective and worth development in countries covered by WHO-recommended maternal care framework.

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Author Contributions. X.Z., D.Y., S.L., and J.Y. contributed in conceptualization of the idea and helped the corresponding author in project administration, data collection and validation, data analysis, and data interpretation. X.Z. wrote the first draft of the manuscript and was mainly responsible for the designation of methodology. D.Y. was responsible for data management and completed the main part of data analysis. S.L. contributed to the design of the protocol for data collection and data analysis and did the majority of visualization of the data. J.Y. was responsible for the major part of project administration and designed and executed the validation of protocol and data. D.Y., S.L., and J.Y. did critical revision to the draft of the manuscript and edited the manuscript. H.Y. and X.G. contributed to data collection, data interpretation, and the discussion of the manuscript. The following members of the CARNATION Study Group (F.L., X.R., X.X., D.Z., J.H., Z.Z., T.Y., J.Z., Q.H., H.K., Z.L., G.Q., D.C., S.Y., Y.W., J.N., T.P., Q.Z., Y.S., M.L., Y.Z., and B.Y.) also contributed to data collection, data interpretation, and the discussion of the manuscript, and B.Y. contributed to fund acquisition. W.B., L.G., and A.D. mainly contributed to the study design, data interpretation, and did critical revision of the manuscript. J.W. mainly contributed to study design, funding and resources acquisition, project administration and supervision, data interpretation, discussion of results, and critical revision of the manuscript. All authors read and approved the final version. J.W. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDIX

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