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Health care and risk of adverse pregnancy outcomes among diabetic women: an updated meta-analysis

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Abstract

Purpose Diabetic women appear to have adverse pregnancy outcomes. Although there were two meta-analyzes that examined the association between health care and adverse pregnancy outcomes, their results were limited because they only included congenital anomaly and perinatal mortality, and they did not clarify the detailed situations of diabetes and health care. This meta-analysis aims to completely evaluate the effects of health care in improving adverse pregnancy outcomes among diabetic mothers.

Methods CNKI, EMBASE, Web of Science, and PubMed databases were searched for eligible studies up to December 2017, without any restrictions. Relevant cohort studies characterizing the relationship between health care and adverse pregnancy outcomes were selected for inclusion in the meta-analysis. We also screened the reference list of relevant studies. The fixed-effect models or random-effect models were used to calculate the risk estimates. The potential sources of heterogeneity were explored by stratified and sensitivity analyzes.

Results Twenty-one studies with 6685 cases were included in our analysis. Health care was associated with significantly decreased risk of congenital anomaly (RR 0.237; 95% CI 0.166–0.338), perinatal death (RR 0.457; 95% CI 0.294–0.712), large for gestational age (LGA) (RR 0.794; 95% CI 0.640–0.986), and neonatal hypoglycemia (RR 0.672; 95% CI 0.486–0.929). Publication bias was not found in most results, with the exception of congenital anomaly and small for gestational age (SGA).

Conclusion Health care is associated with decreased risk of congenital anomaly, perinatal death, LGA, neonatal hypoglycemia.

Keywords Adverse outcomes · Diabetes · Health care · Meta-analysis

Introduction

Maternal diabetes has been a worldwide concern for several decades. Also, it is classified into two kinds of diabetes according to the period of the onset of symptoms and the etiology, including pregestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM). PGDM refers to diabetes among pre-pregnancy women, including type 1 diabetes (T1DM) and type 2 diabetes (T2DM). GDM is a condition where women without diabetes have a high blood glucose level during pregnancy.

In 2017, IDF DIABETES ATLAS Eighth edition reported that 1 in 6 live births were affected by hyperglycemia during pregnancy [1]. As a well-established risk factor, many studies concluded that maternal diabetes was associated with the risk of adverse pregnancy outcomes, such as preterm labor, miscarriage, pre-eclampsia, fetal malformation, macrosomia,

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and perinatal mortality [2, 3]. Metcalfe et al.'s [4] study indicated that the rate of neonatal morbidity was 8.7%, 11.0%, 17.4%, and 24.1% in women of non-diabetes, GDM, T1DM, and T2DM in Canada, respectively. We also found that the rate of neonatal morbidity among women with T1DM and GDM significantly increased from 2004 to 2015 [4]. In addition, Nina et al.'s [5] national cohort study conducted in Denmark suggested that the prevalence of congenital heart disease in offspring among mothers with PGDM was 318/10,000 while the baseline risk was 80/10,000.

Controlling blood glucose concentration during pregnancy was considered as an important measure to reduce the occurrence of adverse pregnancy outcomes. In particular, Hoet et al. [6] proposed that we should improve the "transitory hyperglycemia of pregnancy" by insulin to guard against the "meta-gestational diabetes" in mother and metabolic consequences in the infant. To date, there are two important ways to control blood glucose concentration for diabetic women. Pre-pregnancy care (PPC) is that diabetic women begin to take measures to modify risk factors and optimize glycemic control before pregnancy [7], while care after conception (CC) is that diabetic women begin to take measures to modify risk factors and optimize glycemic control after conception. So far, more and more pregnant women with diabetes were recommended to accept health care (PPC or CC), but the preventive effects of various adverse neonatal outcomes that could be attributed to maternal hyperglycemia remain uncertain. Although there were two meta-analyzes having assessed the relationship of PPC and adverse pregnancy outcomes, the results were limited because the two previous reviews only included congenital anomaly and perinatal mortality, and they did not clarify the detailed situations of diabetes (e.g., PGDM or GDM) and the detailed period (e.g., PPC or CC) that women with diabetes accepted health care at the first time [8, 9]. In addition, the previous reviews included case–control studies that are prone to bias the results. In recent years, a series of new researches on health care and adverse pregnancy outcomes were published, and the number of cohort studies related to this topic was enlarged. In views of the pre-specified situations, it is necessary to incorporate the previous and current evidence and to conduct a comprehensive assessment of the association between health care and adverse pregnancy outcomes. Hence, we conducted an updated meta-analysis to assess the effects of health care in improving adverse pregnancy outcomes among diabetic mothers.

Methods

Study selection

We first searched the electronic databases of EMBASE, Web of Science, PubMed, CNKI up to December 2017 and then screened the reference lists of relevant studies. The following search terms were used: (hyperglycemia, diabet*, pregnancy in diabetics) AND (preconception, pregestational, periconception, preconception*, prepregnancy) AND (service*, counsel*, program*, care, education*, clinic*) AND (cohort, prospective, longitudinal), without any search restrictions.

Studies that met the following inclusion criteria were included in our analyzes: (1) it has a cohort design; (2) the non-exposed group was that reproductive-aged women with PGDM or GDM who did not accept any health care (i.e., PPC and CC) before and during pregnancy; (3) the exposed group was that reproductive-aged women with PGDM or GDM who accepted health care before and during pregnancy; (4) the outcomes of interest were adverse pregnancy outcomes, including congenital anomaly related to maternal diabetes, neonatal death, perinatal death (fetal death after 28th week of gestation and up to 1 week after birth), hypoglycemia (less than 35 mg/dl), respiratory distress syndrome, neonatal intensive care, lager for gestational age (LGA) (birth weight ≥ 4 kg for term infants or birth weight ≥ 90th percentile for the gestation age), small for gestational age (SGA) (birth weight below the 10th percentile for the gestational age), and shoulder dystocia; and (5) relative risks (RRs) with 95% confidence intervals (CIs) were used as a measure of association between health care and adverse pregnancy outcomes (PPC or CC). Studies that met the following criteria were excluded: (1) the non-exposed group was missing; 2). it was a conference presentation or abstract; (3) it was a review or meta-analysis; and (4) it duplicated the same data.

Data extraction and studies assessment

Three authors independently abstracted the information from each included study, such as first author's name, publication year, geographic region, types of outcomes and interventions, and the participants information. The Newcastle Ottawa Scale (NOS) was used to assess the quality of the included cohort studies. Finally, studies inclusion and data extraction were consistent in all reviewers.

Statistical analysis

Between-study heterogeneity was assessed using the I^2 statistic. Fixed-effects models or random-effects models were applied to calculate the risk estimates according to whether there was heterogeneity across studies. The visual inspection of Begger funnel plots and Egger linear regression test were performed to detect publication bias. We conducted stratified analysis by dividing diabetes into different types of diabetes and by dividing health cares into specific health care to explore the association between health care and specific adverse pregnancy outcomes among women with different types of diabetes. Also, we performed sensitivity analyzes to examine the robustness of the results by omitting one study in turn. In the present study, all statistical analyzes were performed in Stata 12.0. The significance level was set at $P<0.05$, unless otherwise specified.

Results

Search results and study characteristics

We retrieved 2163 citations from the electronic databases, and 3 additional citations were indentified through screening the reference lists of relevant studies; of which, 2136 studies were excluded after the first screening of title and abstract. After reviewing the full texts, nine studies were further excluded, and the reasons for excluding them were shown as follows: (1) five [10–14] studies were excluded because the non-exposed group did not meet the inclusion criteria; (2) two [15, 16] studies were case–control studies; and (3) two [17, 18] studies' outcomes were not the pre-specified neonatal outcomes. Finally, 21 publications involving 25 independent cohorts were included in the meta-analysis (Four publications separately reported two independent cohorts [19–22]) (Fig. 1).

Of the 21 studies included in the meta-analysis, four studies were conducted in England [23–26], four in USA [27–30], five in China [31–35], one in Spain [36], one in India [19], one in Ireland [37], one in Australia [20], one in Denmark [21], one in Israel [38], one in France [22], and one in Finland [39]. The main characteristics of the included studies are shown in Table 1.

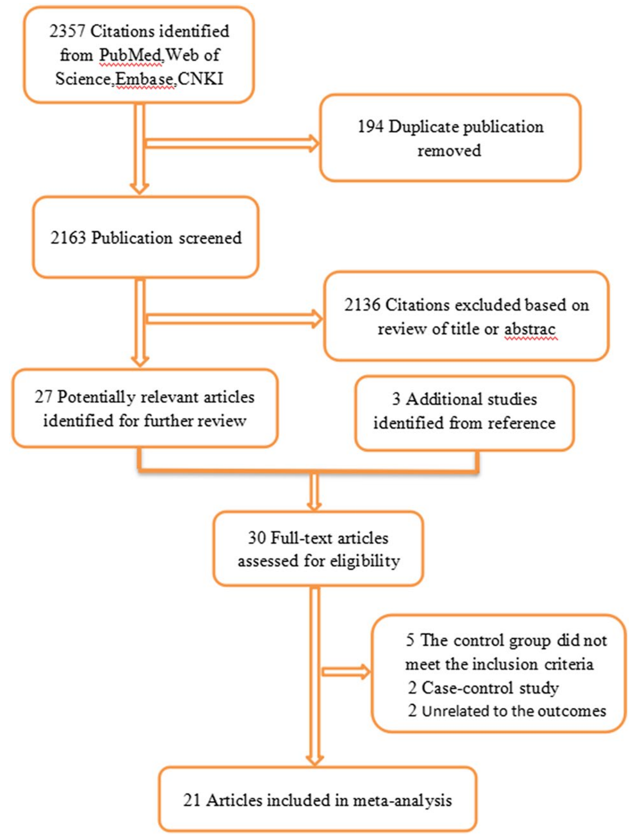

Fig. 1 Review and selection of literature

Congenital anomaly

The association between health care and congenital anomaly was investigated in 19 publications with a total of 22 independent cohorts [19–31, 33–36, 38, 39]. However, we excluded two studies because the number of congenital anomaly in both exposed and non-exposed groups were zero [26, 34]. The results suggested that the risk of congenital anomaly among diabetic women with health care was significantly reduced (RR 0.237, 95% CI 0.166–0.338) compared with that of diabetic women without health care, without substantial heterogeneity ($I^2=0.0\%$, $P=0.689$). Furthermore, we separately performed stratified analysis by T1DM and T2DM, PGDM and GDM, and PPC and CC. For PGDM and GDM, women who accepted health care were less likely to develop congenital anomaly than those who did not (PGDM: RR 0.241; 95% CI 0.165, 0.351, GDM: RR 0.200; 95% CI 0.070, 0.576). For T1DM and T2DM, T1DM women who accepted health care had a lower risk of congenital anomaly than those who did not (RR 0.210, 95% CI 0.125, 0.353); however, the reduced risk was not found among T2DM women with health care (RR 0.649, 95% CI 0.148, 2.858). For PPC and CC, both PPC and CC were associated with a significantly reduced risk of congenital anomaly (PPC: RR 0.269; 95% CI 0.183, 0.394, CC: RR 0.137; 95% CI 0.053, 0.354) (Table 2).

Perinatal death

The perinatal death was reported in six publications [19, 20, 22, 24, 32, 36]. Of these, three studies separately included two independent cohorts [19, 20, 22]. Diabetic women who accepted health care had a significantly decreased risk of perinatal death (RR 0.412 95% CI 0.245, 0.693) as compared to those who did not, with little heterogeneity ($I^2=25.5\%$, $P=0.217$). Stratified analyzes were performed by pre-specified factors. For T1DM, PGDM, and GDM women, those who accepted health care were less likely to experience perinatal death than those who did not (T1DM: RR 0.198; 95% CI 0.059, 0.661, PGDM: RR 0.493; 95% CI 0.291, 0.834, and GDM: RR 0.367; 95% CI 0.164, 0.819), while the reduced risk did not persist in women with T2DM (RR 1.561 95% CI 0.635, 3.838). Also, women who accepted CC experienced a lower risk of perinatal death than those who

Table 1 Overview of cohort studies included in the meta-analysis

References	Location	Type of diabetes	The first intervention time	type of intervention	Type of outcome	Risk of bias (notes)
Steel et al. [23]	England	T1DM	Preconception	A, B, D, E, G	①	6 star
Rosa et al. [36]	Spain	T1DM	Preconception	A, B, C	①④⑤⑥⑦⑧	7 star
Banerjee et al. [19]	India	PGDM and GDM	Pregnancy	A, B	①④⑤⑦	5 star
HELEN et al. [24]	England	T1DM and T2DM	Pregnancy	A, B, D, E, F, G	①②③⑦⑧	6 star
Roman et al. [27]	USA	T1DM and T2DM	Preconception	NA	①	7 star
Rosenn et al. [28]	USA	T1DM	Preconception	A, F	①	6 star
Kekalainen et al. [39]	Finland	T1DM	Preconception	NA	①④⑤⑦⑨	6 star
Neff et al. [37]	Ireland	T1DM	Preconception	A	⑦⑧	6 star
ROSEMARY et al. [25]	England	T1DM	Preconception	A, C, E, F, G, M	①⑦	6 star
M.BETH et al. [30]	USA	T1DM and T2DM	Preconception	NA	①②	6 star
Vincent et al. [20]	Australia	T1DM and T2DM	Preconception	A, D, E,	①⑥⑦⑧	6 star
Yue-mei Chen [32]	China	GDM	Pregnancy	B, C, G	①⑧	5 star
Lin Ye et al. [33]	China	GDM	Pregnancy	A, B	①⑤⑦	5 star
HuilanWang et al. [34]	China	GDM	Pregnancy	A, B	①④⑤⑦	5 star
Yu wang et al. [35]	China	GDM	Pregnancy	A, B	①④⑤⑦	5 star
LiBingluo et al. [31]	China	GDM	Pregnancy	A, B	①⑦	5 star
Damm et al. [21]	Denmark	T1DM	Preconception	A, D	①	8 star
Kitzmiller et al. [29]	USA	T1DM and T2DM	Preconception	A, B, C, D, G	①	5 star
Goldman et al. [38]	Israel	T1DM	Preconception	A, B, C, D, G	①	5 star
Boulot et al. [22]	France	T1DM and T2DM	Preconception	A, B, C, D, G, F	①③	7 star
Dunne et al. [26]	England	T1DM	Preconception	NA	①⑦⑧	6 star

① Congenital anomaly related to maternal diabetes, ② neonatal death, ③ perinatal death, ④ hypoglycaemia, ⑤ respiratory distress syndrome, ⑥ neonatal intensive care, ⑦ LGA, ⑧ SGA, ⑨ shoulder dystocia

A glycemic control by insulin, *B* glycemic control by diet, *C* self monitoring of blood glucose level, *D* contraception until blood glucose is optimized, *E* quit smoking, *F* intake of folic acid, *G* education and/or treatment about diabetes complications, *NA* there was blood glucose control, but the specific measures were unknown

did not (CC: RR 0.375 95% CI 0.204, 0.688). There was no statistically significant difference in the risk of perinatal death between diabetic women with PPC and those without (PPC: RR 0.579 95% CI 0.301, 1.114) (Table 2).

Neonatal death

Five studies presented the outcomes of neonatal death, and all participants were women with PGDM [24–26, 30, 35]. Of the five included studies, one [35] study was further excluded because of lacking of the outcomes of interest. Diabetic women who accepted health care had not a significantly decreased risk of neonatal death (RR 0.405, 95% CI 0.106, 1.539) when compared with those who did not, without heterogeneity ($I^2 = 0.0\%$, $P = 0.996$). Stratified analyzes by pre-specified factors indicated that diabetic women accepted CC (RR 0.411, 95% CI 0.092, 1.836) and PPC (RR 0.382 95% CI 0.020, 7.350) were not associated with a decreased risk of neonatal death when compared with those who did not (Table 2).

Neonatal intensive care

Two publications including three independent cohorts showed the information of neonatal intensive care. All participants were women with PGDM (i.e. T1DM or T2DM), and health care was PPC [20, 36]. The association between neonatal intensive care and health care was not significant (RR 0.671, 95% CI 0.199, 2.268). Stratified analyzes by pre-specified factors suggested that health care did not reduce the risk of neonatal intensive care for T1DM (RR 0.368, 95% CI 0.065, 2.073), T2DM (RR 1.938, 95% CI 0.522, 7.190), and PGDM (RR 0.671, 95% CI 0.199, 2.268) (Table 2).

Respiratory distress syndrome

Nine independent studies reported the relationship of health care and respiratory distress syndrome [19, 31–36, 39]. Meta-analysis showed that health care did not reduce the risk of respiratory distress syndrome (RR 0.686, 95% CI (0.457, 1.032), with moderate heterogeneity ($I^2 = 49.5\%$, $P = 0.045$). Stratified analysis by pre-specified factors indicated that

Table 2 Results of meta-analysis

Type of outcome	Overall RR (95% CI)	T1DM RR (95% CI)	T2DM RR (95% CI)	Pregestational diabetes mellitus (PGDM) RR (95% CI)	Gestational diabetes mellitus (GDM) RR (95% CI)	Prepregnancy care (PPC) RR (95% CI)	Care after conception (CC) RR (95% CI)
Congenital anomaly	0.237 (0.166, 0.338)[f]; I^2=0.0%, P=0.689	0.210 (0.125, 0.353)[f]; I^2=0.0%, P=0.892	0.649 (0.148, 2.858)[f]; I^2=0.0%, P=0.813	0.241 (0.165, 0.351)[f]; I^2=0.0%, P=0.758	0.200 (0.070, 0.576)[f]; I^2=32.1%, P=0.220	0.269 (0.183, 0.394)[f]; I^2=0.0%, P=0.793	0.137 (0.053, 0.354)[f]; I^2=0.8%, P=0.411
Perinatal death	0.457 (0.294, 0.712)[f]; I^2=25.6%, P=0.216	0.198 (0.059, 0.661)[f]; I^2=17.3%, P=0.299	1.561 (0.635, 3.838)[f]; I^2=0.0%, P=0.982	0.493 (0.291, 0.834)[f]; I^2=39.7%, P=0.127	0.367 (0.164, 0.819)[f]; I^2=0.0%, P=0.791	0.579 (0.301, 1.114)[f]; I^2=53.0%, P=0.075	0.375 (0.204,0.688)[f]; I^2=0.0%, P=0.984
Neonatal death	0.405 (0.106,1.539)[f]; I^2=0.0%, P=0.996	0.420 (0.051,3.448)[f]; I^2=0.0%, P=0.806	N/A	0.405 (0.106, 1.539)[f]; I^2=0.0%, P=0.996	N/A	0.411 (0.092, 1.836)[f]; I^2=0.0%, P=0.970	0.382 (0.020, 7.350)[f]; I^2= N/A, P = N/A
Neonatal intensive care	0.671 (0.199, 2.268)[r]; I^2=62.7%, P=0.069	0.368 (0.065, 2.073)[r]; I^2=63.2%, P=0.099	1.938 (0.522, 7.190)[r]; I^2=N/A, P = N/A	0.671 (0.199, 2.268)[r]; I^2=62.7%, P=0.069	N/A	0.671 (0.199, 2.268)[r]; I^2=62.7%, P=0.069	N/A
Respiratory distress syndrome	0.686 (0.457, 1.032)[f]; I^2=49.5%, P=0.045	0.902 (0.510, 1.595)[f]; I^2=0.0%, P=0.959	N/A	1.159 (0.682, 1.967)[f]; I^2=46.6%, P=0.154	0.370 (0.187, 0.733)[f]; I^2=36.9%, P=0.160	0.902 (0.510, 1.595)[f]; I^2=0.0%, P=0.959	0.547 (0.305, 0.981)[f]; I^2=57.6%, P=0.028
LGA	0.794 (0.640, 0.986)[r]; I^2=56.6%, P=0.004	1.014 (0.849, 1.212)[r]; I^2=0.0%, P=0.421	0.935 (0.468, 1.870)[r]; I^2=N/A, P = N/A	1.024 (0.898, 1.167)[r]; I^2=0.0%, P=0.455	0.537 (0.416, 0.691)[r]; I^2=0.0%, P=0.421	1.009 (0.849, 1.199)[r]; I^2=0.0%, P=0.545	0.521 (0.334, 0.814)[r]; I^2=71.5%, P=0.001
SGA	0.597 (0.354,1.005)[f]; I^2=0.0%, P=0.695	0.679 (0.325,1.419)[f]; I^2=0.0%, P=0.460	0.388 (0.052,2.881)[f]; I^2 = N/A, P =N/A	0.597 (0.354,1.005)[f]; I^2=0.0%, P=0.695	N/A	0.625 (0.314,1.248)[f]; I^2=0.0%, P=0.569	0.561 (0.253,1.243)[f]; I^2 = N/A, P = N/A
Shoulder dystocia	0.432 (0.092,2.037)[f]; I^2= N/A, P = N/A	0.432 (0.092,2.037)[f]; I^2= N/A, P = N/A	N/A	0.432 (0.092,2.037)[f]; I^2= N/A, P = N/A	N/A	0.432 (0.092,2.037)[f]; I^2= N/A, P = N/A	N/A
Neonatal hypoglycemia	0.672 (0.486, 0.929)[r]; I^2=53.7%, P=0.035	0.904 (0.762, 1.072)[r]; I^2=0.0%, P=0.845	N/A	0.899 (0.758, 1.066)[r]; I^2=0.0%, P=0.468	0.599 (0.449, 0.798)[r]; I^2=1.8%, P=0.396	0.904 (0.762, 1.072)[r]; I^2=0.0%, P=0.845	0.595 (0.451, 0.786)[r]; I^2=0.0%, P=0.435

r random-effect model, *f* fixed-effect model

health care did not reduce the risk of respiratory distress syndrome in offspring among T1DM and T2DM women, but it was useful for GDM (RR 0.370, 95% CI 0.187, 0.733). Women who accepted CC had a lower risk of respiratory distress syndrome than those who did not (CC: RR 0.547, 95% CI 0.305, 0.981). However, there was no statistically significant difference in the risk of respiratory distress syndrome between diabetic women who accepted PPC and those who did not (Table 2).

LGA

Thirteen publications with a total of fifteen independent cohorts reported the outcomes of LGA [19, 20, 24–26, 31–37, 39]. Results showed that health care significantly reduced the risk of LGA (RR 0.794 95% CI 0.640, 0.986), with substantial heterogeneity (I^2=56.6%, P=0.004). Stratified analysis by pre-specified factors suggested that health care was effective in reducing the risk of LGA among GDM(RR 0.537, 95% CI 0.416, 0.691) women. Women who accepted CC had a lower risk of LGA than those who did not (CC: RR 0.521, 95% CI 0.334, 0.814) (Table 2).

SGA

Five publications totaling six independent cohorts reported the relationship of SGA and health care in women with PGDM [20, 24, 26, 36, 37]. Meta-analysis suggested that

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health care was not associated with a decreased risk of SGA (RR 0.597, 95% CI 0.354, 1.005) among PGDM women, without heterogeneity ($I^2=0.0\%$, $P=0.695$). Stratified analysis by pre-specified factors also showed that health care was not useful for reducing the risk of SGA among T1DM and T2DM women. In addition, there was no statistically significant difference in the risk of SGA when comparing PGDM women who accepted any health care with those who did not (Table 2).

Shoulder dystocia

Only one study examined the association of shoulder dystocia with health care among diabetic women [39], and the result showed that health care reduced the risk of shoulder dystocia (RR 0.432, 95% CI 0.092, 2.037) among diabetic women (Table 2).

Neonatal hypoglycemia

Seven literatures including eight independent cohorts reported the association between health care and neonatal hypoglycemia [19, 32–36, 39] (Banerjee[19] reported two independent cohorts). The incidence rate of neonatal hypoglycemia among diabetic women who accepted health care was significantly lower than that of diabetic women who did not (RR 0.672, 95% CI 0.486, 0.929; $I^2=53.7\%$, $P=0.035$). Stratified analysis by pre-specified factors indicated that health care significantly reduced the risk of neonatal hypoglycemia among GDM (RR 0.599, 95% CI 0.449, 0.798) women. Also, diabetic women who accepted CC had a lower risk of neonatal hypoglycemia as compared to those who did not (RR 0.595, 95% CI 0.451, 0.786) (Table 2).

Sensitivity analyzes and publication bias

Sensitivity analysis suggested that the pooled estimates were not significantly influenced by omitting one study in turn (data not shown). The visual inspection of funnel plots indicated that there were no potential publication biases except for congenital anomaly and SGA. The Egger linear regression test also yield consistent results (congenital anomaly for $P<0.001$, SGA for $P=0.004$) (Fig. 2).

Discussion

Our meta-analysis of the effects of health care in improving fetal outcomes suggested that health care reduced the risk of congenital anomaly, perinatal death, LGA, and neonatal hypoglycemia in offspring among diabetic mothers by 76.3%, 54.3%, 20.6%, and 32.8%, respectively, when compared with diabetic mothers who did not accepted it. However, health care was not associated with a decreased risk of neonatal death, neonatal intensive care, respiratory distress syndrome, SGA, and shoulder dystocia. We also performed stratified analyzes to examine the association between health care and specific adverse pregnancy outcomes among different kinds of diabetic women. The analyzes stratified by T1DM and T2DM suggested that health care significantly reduced the incidence rate of congenital anomaly and perinatal death in offspring among T1DM mothers; however, it did not reduce the risk of any adverse pregnancy outcomes among T2DM mothers. The analyzes stratified by GDM and PGDM showed that health care was associated with a lower risk of congenital anomaly, perinatal death, respiratory distress syndrome, LGA, and neonatal hypoglycaemia among GDM mothers, while it only reduced the risk of congenital anomaly and perinatal

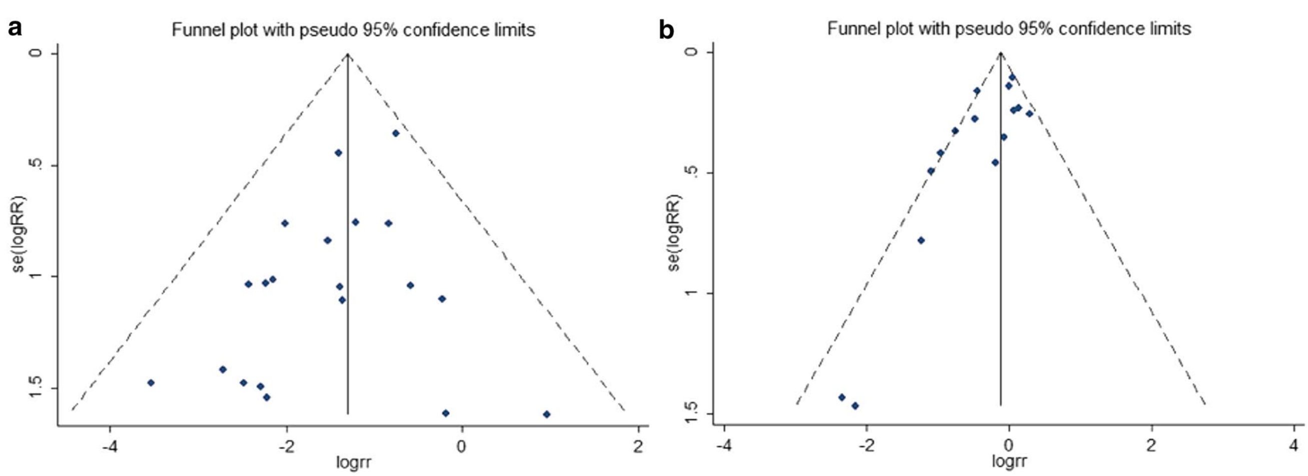

Fig. 2 Funnel plots of congenital anomaly and SGA (**a** congenital anomaly; **b** SGA)

death among PGDM mothers. The stratified analyzes of PPC and CC suggested that PPC was associated with a decreased risk of congenital anomaly among diabetic mothers, while CC was associated with a lower risk of congenital anomaly, perinatal death, respiratory distress syndrome, LGA, and neonatal hypoglycemia. In views of these results, we suggested that health care could reduce the risk of most adverse pregnancy outcomes among diabetic mothers.

Overall, our results are consistent with the two previous reviews. Ray et al. [8] concluded that the rate of major malformations was more lower in offspring among diabetic women with PPC than that of offspring among diabetic women without PPC. A study [9] reported by Wahabi et al. also suggested that PPC reduced the risk of congenital malformation and perinatal mortality but not for SGA. However, there are still some differences in the results between our study and the previous reviews. For example, we included more adverse pregnancy outcomes than the previous reviews, such as neonatal death, neonatal intensive care, shoulder dystocia, LGA, and SGA, which provided more meaningful information; we only considered cohort studies, suggesting that our estimates are precise and robust because cohort studies are less likely to be affected by bias.

The underlying mechanisms involved in the association between hyperglycemia effects and adverse pregnancy outcomes are uncertain. However, the abnormal metabolic environment is widely recognized as the risk factors associated with adverse pregnancy outcomes. Several studies suggested that fetal hyperglycemia leads to abnormal generation of oxygen radicals in cells, which is bad for the vascularization of developing tissues [40–42]. The offsprings of diabetic mothers are more prone to have hyperglycemia because insulin cannot pass through the placenta [43]. Even more compelling is that the placenta's function will be impaired if the hyperglycemia persists [44–46]. In addition, the changed expression of regulating genes in the fetuses of diabetic women may contribute to adverse pregnancy outcomes because it makes the cellular mitosis and programmed cell death abnormal [40, 44, 47]. The abnormality of lipid level is also considered as a risk factor associated with adverse pregnancy outcomes among diabetic women. Ryckman et al. [48] reported that women with GDM would have a higher level of plasma glucose, triglycerides, and non-HDL-C and a lower level of HDL-C when compared with those who without. Graf [49] suggested that LGA was associated with the levels of triglycerides and FFA in mothers.

Moderate heterogeneity was observed between studies, which was not surprising, given the different study populations and methodologies. However, sensitivity analyzes suggested that the pooled estimates were not significantly changed by omitting one study at a time, meaning that our results were robust.

Our meta-analysis has several significant strengths. First, we have included the English and Chinese language literatures in the analysis, meaning that our results are more generalizable. Second, only cohort studies were included in the analysis; so, our results were less likely to be affected by bias. Third, the specific adverse pregnancy outcomes involved in the study were much more than the previous reviews, which provided more meaningful information. Finally, we have comprehensively assessed the association between health care and specific adverse pregnancy outcomes among different kinds of diabetic mothers. However, we should still review the results with caution because all the included studies are observational studies other than interventional studies.

Conclusions

Health care is associated with a reduced risk of congenital anomaly, perinatal death, LGA and neonatal hypoglycemia. It highlights the necessity of heal care in improving adverse pregnancy outcomes among diabetic women. However, given the limited number of studies, more high-quality cohort and interventional studies are required to further evaluate these associations.

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Compliance with ethical standards

Conflict of interest Author Guohong Xie declares that she has no conflict of interest. Author Zan Zheng declares that he has no conflict of interest. Author Taocheng Liu declares that he has no conflict of interest. Author Lulu Qing declares that she has no conflict of interest. Author Xiuqing Hong declares that she has no conflict of interest. Author Wenting Zha declares that she has no conflict of interest. Author Yuan Lv declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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