Continuous subcutaneous insulin infusion vs multiple daily injections in pregnant women with type 1 diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials and observational studies

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Abstract

Background: Randomised controlled trials (RCTs) have shown an advantage of continuous subcutaneous insulin infusion (CSII) over multiple daily injections (MDI) in the general type 1 diabetes mellitus (T1DM) population. RCT data on T1DM management in pregnancy remain limited.

Objective: We performed a systematic review of both RCTs and non-RCTs evaluating CSII vs MDI in T1DM-complicated pregnancy.

Study design: Electronic databases were searched for studies comparing CSII with MDI in T1DM-complicated pregnancy.

Methods: A meta-analysis provided point estimates with 95% confidence intervals (CI). Continuous outcomes were reported as weighted mean differences (WMD) or standardised mean differences (SMD), and dichotomous data as relative risk (RR).

Results: The search identified 47 studies, including 43 non-RCTs, reporting on 7824 pregnancies. The meta-analysis showed a lower HbA1c level with CSII vs MDI in the first trimester (WMD: -0.45% ; 95%CI: -0.62 , -0.27). This difference decreased in subsequent trimesters. Compared to MDI, therapy with CSII resulted in higher gestational weight gain (GWG) (WMD: 1.02 kg; 95%CI: 0.41 , 1.62), and lower daily insulin dose requirements in the first (SMD: -0.46 ; 95%CI: -0.68 , -0.24) and subsequent trimesters. Moreover, infants from the CSII group were more likely to be large for gestational age (LGA) (RR: 1.16 ; 95%CI: 1.07 , 1.24) and less likely to be small for gestational age (SGA) (RR: 0.66 ; 95%CI: 0.45 , 0.97).

Conclusions: In T1DM-complicated pregnancy, CSII compared to MDI therapy resulted in better first trimester glycaemic control; this difference decreased in subsequent trimesters. CSII therapy was associated with lower insulin requirements, higher GWG and altered risk for infants being LGA and SGA.

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Table 1 Methodological characteristics of the studies included in the systematic review.

No.	Study	Number of patients	Number of participants per arm (CSII/MDI)	Country	Publication form	Duration of the study	Study design	Comparator group allocation	Start of CSII
#01	Abell et al. (23)	167	40/127	Australia	Full text	2010–2015	Retrospective	ND	Before pregnancy: 99%
#02	Acosta-Delgado et al. (24)	556	77/479	Spain	Abstract	1990–2014	Retrospective	ND	ND
#03	Bruttomesso et al. (25)	144	100/44	Italy	Full text	2001–2009	Retrospective	Consecutive	Before 6th month of pregnancy
#04	Burkart et al. (13)	89	48/41	Germany	Full text	1979–1986	RCT	Random	≤T1
#05	Chen et al. (26)	90	30/60	Israel	Full text	2003–2006	Retrospective	Matched	Before pregnancy
#06	Cheng et al. (27)	688	60/628	USA	Abstract	2001–2004	Retrospective	ND	ND
#07	Chico et al. (28)	315	103/212	Spain	Full text	1984–2006	Retrospective	Consecutive	Before pregnancy
#08	Chico et al. (29)	1534	324/1210	Spain	Full text	2002–2010	Retrospective	Consecutive	ND
#09	Coustau et al. (14)	22	11/11	USA	Full text	<1986	RCT	Random	Before pregnancy: 68%
#10	Cyganek et al. (30)	269	112/157	Poland	Full text	2000–2008	Retrospective	Consecutive	During pregnancy: 32%
#11	Cypryk et al. (31)	116	30/86	Poland	Full text	2003–2006	Retrospective	Consecutive	Before pregnancy: 37.5% T1: 62.5%
#12	Feldberg et al. (32)	65	28/37	Israel	Full text	1981–1988	Retrospective	Unclear	T1: 53%
#13	Gabbe et al. (33)	60	36/24	USA	Full text	1996–1999	Retrospective	Matched	ND
#14	Giménez et al. (34)	58	29/29	Spain	Full text	1998–2004	Retrospective	Matched	Before pregnancy: 33%
#15	González-Romero et al. (35)	99	35/64	Spain	Full text	1997–2008	Retrospective	Matched	During pregnancy: 67%
#16	Hammond et al. (36)	80	40/40	UK	Abstract	1998–2008	Unclear	Patients decision	Before pregnancy: 93%
#17	Hiéronimus et al. (37)	56	33/23	France	Full text	1999–2003	Retrospective	ND	M1: 7%
#18	Kallas-Koeman et al. (38)	387	129/258	Canada	Full text	2006–2010	Retrospective	Consecutive	Before pregnancy 94%
#19	Kekallainen et al. (39)	135	48/87	Finland	Full text	2000–2012	Retrospective	Consecutive	T2: 6%
#20	Kernaghan et al. (40)	42	18/24	UK	Full text	1998–2005	Prospective	Patients decision	ND
#21	Laatikainen et al. (15)	40	13/27	Finland	Full text	1982–1983	RCT	Random	Before pregnancy: 67%
#22	Lapolla et al. (41)	93	25/68	Italy	Full text	1990–2000	Retrospective	Glycaemic control	T1: 33%
#23	Lewis-Jenkins et al. (42)	28	14/14	UK	Abstract	ND	Retrospective	ND	ND
#24	Lorenzini et al. (43)	98	80/18	France	Abstract	ND	Retrospective	ND	Before pregnancy: 69%
#25	Mathiesen et al. (44)	123	27/96	Denmark	Full text	2009–2011	Retrospective analysis of the RCT data	Population of the RCT study	T1–T3: 31%
#26	Mello et al. (45)	53	35/18	Italy	Full text	2009–2012	Retrospective	ND	Before pregnancy: 96%
#27	Murphy et al. (46)	598	132/466	UK	Abstract	2013	Retrospective	Consecutive	T1: 4%
#28	Neff et al. (47)	464	424/40	Ireland	Full text	2006–2010	Retrospective	Consecutive	Before pregnancy: 100%
#29	Nosari et al. (48)	32	16/16	Italy	Full text	1988–1990	RCT	Random	Before pregnancy: 100%
#30	Quirós et al. (49)	36	16/20	Spain	Full text	2011–2012	Retrospective	Consecutive	Mainly during pregnancy ND

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#31	Rodriguez Rodriguez et al. (50)	29	10/19	Spain	Abstract	2008	Prospective	ND
#32	Roeder et al. (51)	35	ND/ND	USA	Abstract	2007–2010	Retrospective	ND
#33	Salmeen et al. (52)	48	35/13	USA	Abstract	Since 2006	Retrospective	ND
#34	Samoylova et al. (53)	40	18/22	Russia	Abstract	ND	Unclear	ND
#35	Sampanis et al. (54)	26	15/11	Greece	Abstract	ND	Unclear	ND
#36	Saraiva et al. (55)	84	19/65	Portugal	Abstract	Since 2005	Retrospective	ND
#37	Sargent et al. (56)	95	51/44	USA	Full text	2007–2014	Retrospective	ND
#38	Shanmugasundaram et al. (57)	90	52/38	UK	Abstract	2002–2009	Retrospective	ND
								Before pregnancy: 38% During pregnancy: 62%
#39	Silvestre et al. (58)	48	22/26	Portugal	Abstract	2012–2016	Retrospective	ND
#40	Skalli et al. (59)	108	14/94	Canada	Abstract	2000–2009	Retrospective	ND
#41	Smith et al. (60)	108	ND	UK	Abstract	2005–2012	Retrospective	ND
#42	Sperling et al. (61)	156	49/107	USA	Full text	2006–2014	Retrospective	ND
#43	Talaviya et al. (62)	34	14/20	India	Full text	2010–2012	Retrospective	ND
#44	Tiselko et al. (63)	184	91/93	Russia	Abstract	ND	Unclear	ND
#45	Volpe et al. (64)	42	20/22	Italy	Full text	2005–2008	Retrospective	ND
#46	Wender-Ozegowska et al. (65)	128	64/64	Poland	Full text	2004–2009	Retrospective	ND
								Before pregnancy: 100% T1: 100%
#47	Wudi et al. (66)	32	19/13	Hungary	Abstract	ND	Retrospective	ND

M1, first month of pregnancy; ND, not determined; T1, first trimester; T2, second trimester; T3, third trimester.

Introduction

Given that the onset of type 1 diabetes mellitus (T1DM) usually occurs early in life, many women of reproductive age worldwide are affected (1, 2, 3, 4). Recent literature has remarked that the incidence of T1DM is rising (5). Women with pregestational T1DM have an increased risk of adverse clinical outcomes, including spontaneous abortions, foetal malformations, macrosomia, stillbirths, preeclampsia, hydramnios, operative delivery in mothers, and progression of chronic diabetic complications (6). The risk of congenital abnormalities is as high as 25% in women with T1DM who have a HbA_{1c} level above 10%, and remains higher than the risk in the general population, affecting even pregnant patients with moderate hyperglycaemia (7). Fortunately, effective medical care provided to women with pregestational T1DM can foster enhanced glycaemic control and reduce the risk of these complications (8, 9, 10).

New therapeutic and monitoring tools for glycaemic control have become commonly available in recent decades. Currently, two modes of insulin delivery for T1DM patients are widely used. The first is based on multiple daily injections (MDI), which involves several shots of short-acting prandial insulin, along with 1–2 doses of a long-acting basal preparation. The second route is continuous subcutaneous insulin infusion (CSII), which provides a constant supply of insulin via a personal pump with superimposed meal-related boluses (11). In the general T1DM population, it has been shown that when compared with MDI, CSII was associated with a slightly lower HbA_{1c} level and a smaller risk of severe hypoglycaemia (12). Until now, however, only a few small randomised control trials (RCTs) including T1DM pregnant women have been performed, and no firm understanding as to whether either of these treatment methods is advantageous in this particular patient population exists (13, 14, 15). Two comprehensive reviews comparing CSII with MDI in pregnancy complicated by T1DM were in fact recently published. Neither, however, revealed any conclusive results for both glycaemic control and clinical maternal and foetal outcomes, as they were restricted only to RCTs, which were few and underpowered (16, 17).

The aim of our study was to perform a systematic review and meta-analysis based on both randomised and non-randomised data comparing the two methods of insulin therapy in pregnant women with T1DM, with respect to glycaemic control, particularly the HbA_{1c} level, as well as important maternal and foetal endpoints.

Subjects and methods

Eligibility criteria for meta-analysis

Studies were considered relevant for this systematic review if they directly compared CSII with MDI in pregnant women with pregestational T1DM. No restriction was made with respect to the type of insulin used (regular vs analogue), however, studies reporting data on animal insulin or involving less than 10 pregnancies in any group were excluded.

Randomised and observational studies were included if they presented outcomes on glycaemic control or maternal and foetal outcomes, regardless of the type of publication (i.e. full-text paper or conference abstract). Overall we consider 4 glycaemic control parameters (HbA1c level, insulin dose, diabetic ketoacidosis (DKA), severe hypoglycaemic episodes), 3 maternal outcomes (gestational weight gain (GWG), gestational hypertension and preeclampsia) as well as 11 foetal and neonatal endpoints (perinatal death, congenital abnormalities, preterm delivery, macrosomia, delivery of large-for-gestational-age (LGA) infants, delivery of small-for-gestational-age (SGA) infants, hypoglycaemic events, hyperbilirubinemia, shoulder dystocia, respiratory complications, and intensive care unit admission).

Information sources and search strategy

Major medical databases were searched until November 2017, including MEDLINE, EMBASE and CENTRAL, with a high-sensitivity search strategy based on key words referring to the population ('type 1 diabetes mellitus', 'insulin-dependent diabetes mellitus', 'pregestational', 'maternal', 'gestational') and intervention ('continuous subcutaneous insulin infusion', 'insulin pump', 'pump therapy'). To identify recently published studies, abstracts presented at major conferences on diabetes (ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes) were screened, along with clinical trial registries. We also searched the reference lists of included articles and systematic reviews. Two authors independently selected studies for potential inclusion based on title and abstract screening, followed by full-text evaluation, if available. Any disagreements were resolved through discussion.

Data extraction and quality assessment

Data were extracted from the identified studies onto a structured data form by the main author. Its precision was verified independently by an external reviewer not

engaged in the systematic review. All included studies underwent a quality assessment. For RCTs, criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions were used; in particular, each study was analysed in terms of presence of selection, performance, detection, attrition and reporting biases. Additionally, quality assessment based on the Jadad scale was performed (18). For non-RCT studies, the Newcastle-Ottawa Scale (NOS) for quality assessment was used, which takes into account sampling, differences between studied groups and method of outcome assessment (19).

Statistical analysis

Dichotomous outcomes estimates were presented as relative risks (RR), while continuous endpoints were reported as weighted mean differences (WMD) or standardised mean differences (SMD). If heterogeneity between studies existed, data were pooled in meta-analyses using the DerSimonian & Laird method, regardless of type of outcomes; otherwise, the Mantel-Haenszel test for dichotomous outcomes was applied and the inverse variance method was used for continuous endpoints. Heterogeneity between studies was tested using the Cochrane Q test or I^2 statistics and judged relevant when $P < 0.1$ or $I^2 > 50\%$. To explain the source of heterogeneity, a sensitivity analysis was also performed considering the following modifiers: study design (randomised vs observational), type of publication (conference abstract vs full-text article), time of CSII initiation (before or during pregnancy), preconception care (yes or no), type of prandial insulin (human regular insulin vs insulin analogues). The chi-square test for interaction was used to evaluate if the observed effect was consistent between subgroups. Risk of publication bias was evaluated by the Egger and Begg-Mazumdar tests (20). If a risk of publication bias was found, the trim and fill method was used to adjust the funnel symmetry (21, 22).

Results

Study selection

In total, the search of major medical databases yielded 1327 papers, of which 1140 unique records remained after eliminating duplicates. Search of other sources, such as EASD or ADA conference abstracts, led to the inclusion of 1368 records. Five additional articles were found from the reference lists. Based on title and the abstract screening, 134 records proceeded for further full-text analysis, if

available. A total of 69 papers were excluded due to an inadequate population, intervention, method, cohort size, outcome or comparator. Finally, 47 studies (65 records) met the eligibility criteria ([Supplementary Fig. 1](#), see section on [supplementary data](#) given at the end of this article), including 29 full-text papers and 18 conference abstracts. Some studies were published in more than one paper, increasing the number of records in relation to number of studies. In most cases, they were initially published as a conference abstract and then as a full-text article.

Study characteristics

The 47 studies included in this analysis were conducted in 18 countries, with the highest number being performed in the United States of America (8), Spain (7), Great Britain (6), Italy (5), and Poland (3). Among the included studies, there were only 4 RCTs, all of them of a very low quality, with a high risk of systematic bias. They were also all conducted before the year 1990, so the studied standard of care and available diagnostic and therapeutic options for T1DM does not reflect current clinical practice. The remaining 43 studies were observational: 39 were retrospective, 2 were prospective and no information about the study design was given for the remainder.

In 21 studies, no information about the allocation was given; 6 reports matched patients in the studied groups, while 12 included all eligible patients identified during a study period. Allocation to the MDI or CSII group based on glycaemic control was applied in 2 studies, while in 3 others, the choice of therapy was left to the patient ([Table 1](#)).

Quality assessment with the NOS showed a wide variety between the observational studies, ranging from 4 to 9 points, which stemmed mainly from the publication form. Most full-text papers received between 6 and 9 points (median 7), while the median for conference abstracts was only 5 (range: 4–6 points).

Of the 47 studies that met the inclusion criteria, 7824 pregnancies were reported, including 2651 women on CSII and 5030 on MDI. In two papers (143 patients), no information about group sizes was given. Overall, both arms were well-balanced in terms of age, microangiopathy and hypertension, while some differences regarding T1DM duration, baseline glycaemic control and preconception care existed. Means or medians of disease duration were reported in 31 studies. In the CSII group, they ranged from 8.2 to 22 years, compared to a range of 6.9 to 18.7 years in the MDI group. In 15 out of 31 studies in which the duration of T1DM was presented, the CSII group was characterised by a longer time course of disease, while no differences were

seen in another 15 studies; in only 1 report did the CSII group have a shorter disease duration on average.

Prepregnancy HbA_{1c} levels were reported in 24 studies; however, only 21 of them provided the difference between the groups. A total of 8 papers reported lower prepregnancy HbA_{1c} levels in the CSII group, 1 reported the opposite and no differences were reported in the remaining, although non-significantly lower values were seen for CSII. Preconception care was reported in 19 papers; however, comparison between the studied groups was possible in only 16 papers. In 12 of these 16 papers, the percentage of those who received preconception care was significantly higher in the CSII group; the difference was not significant in the remaining 4 papers, although a tendency towards CSII could be seen in 3 of them.

Different insulin types were used in the included papers. The CSII group used regular human insulin (RHI) or rapid-acting insulin analogues (RAA). Those in the MDI group performed at least 4 injections, 3 of which were postprandial (RHI or RAA), and 1 or 2 of which were basal insulin (mostly NPH). Information about the glucose monitoring method was reported in 23 studies. In all of them, self-monitoring of blood glucose (SMBG) was used, and in 3 studies, SMBG was used together with continuous glucose monitoring (CGM). Nine studies only included women who started CSII before pregnancy, and 2 studies only included women who initiated pump therapy during the first trimester. In 15 papers, the population encompassed women who initiated CSII either before pregnancy or during the first trimester, while no information about CSII initiation was presented in 23 studies ([Table 2](#)).

Synthesis of results

HbA_{1c} level

A meta-analysis of the 24 trials (3104 pregnancies) reporting on the first trimester HbA_{1c} level revealed almost 0.5% lower level in the CSII group than in the MDI group (WMD: −0.45 95% CI: −0.62, −0.27; [Fig. 1](#)); however, significant heterogeneity existed between the studies ($I^2=78\%$). The subgroup analysis showed that the magnitude of the effect size when compared to the MDI group was higher in women who started pump therapy before pregnancy (WMD −0.60%; 95%CI −0.97, −0.24; [Supplementary Fig. 21](#)) than in those who did it during the first trimester (WMD −0.35%; 95%CI −0.92, 0.22; [Supplementary Fig. 22](#)). The HbA_{1c} level in the second trimester was reported in 18 studies, encompassing 1902 pregnancies. The CSII group showed lower HbA_{1c} level, with WMD in relation to the comparator group

Table 2 Population characteristics of the studies included in the systematic review.

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Clinical Study			P M Rys, A H Ludwig-Słomczynska and others		CSII and MDI in T1DM-complicated pregnancy		178:5		551	
#22	Lapolla et al. (41)	25/68	31.6 vs 30.2; (NS)	16.0 vs 11.6; (P<0.04)	7.7 vs 7.2 (NS)	52% vs 25%; (P<0.026)	44% vs 15%; (P=0.007)	4% vs 3%	ND	
#23	Lewis-Jenkins et al. (42)	14/14	ND	ND	ND	ND	ND	ND	ND	
#24	Lorenzini et al. (43)	80/18	ND	ND	6.8 vs 7.65 vs 7.5 (P<0.003)	ND	ND	ND	ND	
#25	Mathiesen et al. (44)	27/96	ND	16 vs 13; P=0.05	ND	ND	44% vs 24%; (P=0.05)	ND	ND	
#26	Mello et al. (45)	35/18	33.6 vs 31.4 (NS)	15.4 vs 13.4 (NS)	ND	46% vs 22%; (P=0.09)	17% vs 17% (NS)	3% vs 0% (NS)	ND	
#27	Murphy et al. (46)	132/466	31.5 vs 29.4	16.7 vs 14	ND	ND	ND	ND	ND	
#28	Neff et al. (47)	424/40	35 vs 31; (P<0.001)	22 vs 13; (P<0.001)	ND	40% vs 13%; (P<0.001)	ND	ND	ND	
#29	Nosari et al. (48)	16/16	25.5 vs 27 (NS)	From 3 to 16	ND	12.5%	13% vs 19% (NS)	19% vs 13% (NS)	ND	
#30	Quirós et al. (49)	16/20	ND	ND	(NS)	ND	ND	ND	ND	
#31	Rodriguez Rodriguez et al. (50)	10/19	ND	ND	HbA _{1c} > 7%; 20% vs 47%	ND	ND	ND	ND	
#32	Roeder et al. (51)	ND	ND	ND	NS	ND	ND	ND	ND	
#33	Salmeen et al. (52)	35/13	25 vs 32.9; (P= <0.001)	9.2 vs 18.7 (P<0.05)	ND	ND	ND	ND	ND	
#34	Samoylova et al. (53)	18/22	22.3 vs 23.1 (NS)	ND	7.93 vs 7.75	ND	ND	ND	ND	
#35	Sampanis et al. (54)	15/11	ND	ND	ND	ND	ND	ND	ND	
#36	Saraiva et al. (55)	19/65	30.4 vs 29.3 (NS)	17 vs 11.7; P=0.006	8 vs 7.9 (NS)	84% vs 52%; (P=0.02)	NS	NS	ND	
#37	Sargent et al. (56)	51/44	ND	ND	ND	ND	ND	ND	ND	
#38	Shanmugasundaram et al. (57)	52/38	31.9 vs 29.9; (P=0.1)	17 vs 10.7; P<0.001	ND	ND	ND	ND	ND	
#39	Silvestre et al. (58)	22/26	33 vs 30 (NS)	16 vs 15 (NS)	7.8 vs 10.1 (P<0.05)	ND	ND	ND	ND	
#40	Skalli et al. (59)	14/94	ND	21.2 vs 13.9; (P=0.0004)	ND	ND	NS	NS	ND	
#41	Smith et al. (60)	108	32	16	6.5 vs 7.6; (P=0.006)	59%	ND	ND	ND	
#42	Sperling et al. (61)	49/107	30.2 vs 26.4 (P<0.001)	8.2 vs 6.9 (P=0.02)	ND	ND	ND	ND	ND	
#43	Talaviya et al. (62)	14/20	31.3 vs 30.2; (P=0.44)	8.5 vs 8.35; (P=0.95)	ND	ND	NS	NS	ND	
#44	Tiselko et al. (63)	91/93	(NS)	14.3 vs 12.8 (NS)	7.2 vs 7.9 (NS)	ND	ND	ND	ND	
#45	Volpe et al. (64)	20/22	31 vs 29.8 (NS)	16.8 vs 12.1; (P=0.06)	ND	50% vs 18% (IS)	35% vs 14%; (P=0.057)	10% vs 0%	ND	
#46	Wender-Ozegowska et al. (65)	64/64	27.5 vs 27.2 (NS)	14.4 vs 14.8 (NS)	ND	ND	22% vs 19% (NS)	13% vs 16% (NS)	13% vs 5% (NS)	
#47	Wudi et al. (66)	19/13	29.9 vs 30.3 (NS)	15.4 vs 8.3 (P<0.05)	NS	ND	53% vs 8% (P<0.05)	ND	ND	

LP, lispro insulin; ND, not determined; NS, not significant; RHI, regular human insulin.

LP, lispro insulin; ND, not determined; NS, not significant; RHI, regular human insulin.

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reaching -0.25% (95%CI $-0.38, -0.12$; Fig. 2). Twenty-three papers, encompassing 2696 pregnancies, reported on the HbA1c level in the third trimester. In the CSII arm, the HbA1c level was lower than that in the MDI group (Fig. 3); however, the difference between groups was not significant (WMD -0.09% ; 95%CI $-0.20, 0.02$). Similar to the analysis of the first trimester, significant heterogeneity between studies was also observed in the second ($I^2=59\%$) and third ($I^2=64\%$) trimester. The cause of this heterogeneity was not identified.

Episodes of severe hypoglycaemia

Data regarding episodes of severe hypoglycaemia during pregnancy were available in 18 studies and included 3431 pregnancies (Supplementary Fig. 2). No difference was found between the CSII and MDI groups with respect to the percentage of patients suffering from severe hypoglycaemia (RR 0.85, 95%CI 0.67, 1.07). The obtained results were very homogeneous ($I^2=0\%$).

Diabetic ketoacidosis

The meta-analysis of 17 studies involving 2087 pregnancies demonstrated that the percentage of patients with DKA was low and comparable between arms (RR 1.27, 95%CI 0.72, 2.24). No significant heterogeneity was observed in this analysis (Supplementary Fig. 3).

Insulin dose Overall, 15 studies provided data regarding insulin dose in the first trimester. In 8 papers, the total daily dose was available, while the remaining 7 reported insulin dose per body weight (IU/kg). Pooled results of all studies (regardless of the type of data) showed lower insulin requirements in women with T1DM on CSII therapy than in those on MDI therapy (SMD -0.46 ; 95%CI $-0.68, -0.24$) (Supplementary Fig. 4). Second trimester insulin dose was available in 6 studies, 2 of which reported total daily dose and 4 reported total insulin dose per body weight. The meta-analysis of all studies showed a lower insulin requirement in the CSII group (SMD -0.49 ; 95%CI $-0.69, -0.28$) (Supplementary Fig. 5). Thirteen studies reported on the mean daily insulin dose in the third trimester, of which 8 presented data regarding total insulin dose per body weight, while the remaining 5 presented the total daily insulin dose per patient. The meta-analysis of the 13 papers (Supplementary Fig. 6) showed lower insulin requirements in the CSII group (SMD -0.39 ; 95%CI $-0.65, -0.13$).

Maternal outcomes

Pooled results revealed no significant differences between CSII and MDI therapy with respect to gestational hypertension (11 studies; RR 0.91; 95%CI 0.70, 1.18; Supplementary Fig. 7), as well as preeclampsia (16 studies, RR 1.06; 95%CI 0.69, 1.61; Supplementary Fig. 8). Information regarding absolute GWG (in kilograms) was published in 12 studies, encompassing 1364 pregnancies. Meta-analysis of these 12 studies did not show a difference between CSII and MDI therapy (WMD $=0.61$ 95%CI $-0.19, 1.42$), although high heterogeneity of the studies was observed ($I^2=46\%$), likely resulting from data published by a Spanish group (35) that suggested lower GWG in the CSII arm (mean difference -2.0 kg 95%CI $-3.70, -0.30$), while most other papers reported the reverse trend. When the Spanish paper was excluded from the meta-analysis, the cumulative results of the 11 other papers showed that GWG was approximately 1.0 kg higher in the CSII group than in the MDI group (WMD 1.02 kg; 95%CI 0.41, 1.62) (Fig. 4). This difference was significant and without between-study heterogeneity ($I^2=0\%$).

Foetal and neonatal outcomes

A meta-analysis of 14 studies revealed significantly higher risk of spontaneous abortion in women using CSII than in those on MDI (RR 1.79; 95%CI 1.51, 2.12) without statistical heterogeneity (Supplementary Fig. 9). Other foetal complications, including perinatal death, congenital anomalies and preterm delivery, were reported in 19, 28 and 26 studies, respectively, and none of them revealed significant differences between CSII and MDI therapy (Supplementary Figs 10, 11 and 12). Pooled results of all studies meeting inclusion criteria showed no significant differences between CSII and MDI therapy with respect to perinatal deaths (RR 0.83; 95%CI 0.55, 1.25), congenital defects (RR 1.14; 95%CI 0.92, 1.41) and preterm delivery (RR 1.07; 95%CI 0.97, 1.17).

The pooled results of 27 homogenous studies ($I^2=13\%$) revealed that the percentage of LGA neonates, mainly defined as birth weight $\geq 90\%$ percentile, was higher in the CSII group when compared to the MDI group (RR 1.16; 95%CI 1.08, 1.25; Fig. 5). Macrosomia, in most papers defined as birth weight ≥ 4000 g, was also more prevalent in the CSII group than the MDI group (19% vs 23%), but this difference did not reach statistical significance (RR 1.13; 95%CI 0.93, 1.38; Supplementary Fig. 13), and may be at least partially explained by a high degree of heterogeneity ($I^2=55\%$). However, the cumulative results of 2 studies

Figure 1
 Forest plot of the meta-analysis for the first trimester HbA1c level in pregnant women with T1DM receiving CSII vs MDI therapy.

showed higher risk of birth weight above 4500g in the CSII group than the MDI group (RR 2.51; 95%CI 1.20, 5.21; [Supplementary Fig. 14](#)). On the other hand, the probability of infants being born SGA was lower in the CSII group than the MDI group (RR 0.66; 95%CI 0.45, 0.97; [Supplementary Fig. 15](#)). No significant differences were found between both methods of insulin delivery with respect to other foetal complications, including neonatal hypoglycaemia (RR 1.12; 95%CI 0.97, 1.28; [Supplementary Fig. 16](#)), hyperbilirubinemia (RR 1.00; 95%CI 0.83, 1.19; [Supplementary Fig. 17](#)), shoulder dystocia (RR 1.15; 95%CI 0.70, 1.89; [Supplementary Fig. 18](#)), respiratory

complications (RR 0.90; 95%CI 0.71, 1.13; [Supplementary Fig. 19](#)) and intensive care unit admission (RR 0.93; 95%CI 0.80, 1.09; [Supplementary Fig. 20](#)).

Sensitivity analysis

A sensitivity analysis showed that, in most cases, differences between studies with respect to their design, type of publication, moment of CSII initiation and type of prandial insulin did not explain the heterogeneity observed in the meta-analysis, with 1 exception regarding the first trimester HbA1c level, described

Figure 2

Forest plot of the meta-analysis for the second trimester HbA1c level in pregnant women with T1DM receiving CSII vs MDI therapy.

earlier. Additionally, a meta-analysis including only full-text papers resulted in a reduction of heterogeneity for 3 outcomes (preeclampsia, macrosomia and neonatal hypoglycaemia), but no interaction between abstracts and full-text papers was observed. We also intended to perform a subgroup analysis with respect to the preconception care; however, only 1 study (47) reported a subgroup analysis with respect to this variable, with the remaining papers reporting data collectively on women, regardless of whether they received preconception care.

As mentioned earlier, the sensitivity analysis did not reveal any interaction between RCTs and observational studies; however, it should be noted that only 4 RCTs with a small sample size were identified, while all remaining studies were of an observational design (including more than 7000 pregnancies in total). Therefore, a subgroup meta-analysis restricted to the observational studies revealed similar results to the base case scenario (involving both RCTs and non-RCTs), while the pooled data of RCTs did not show any difference between the studied groups for any of the analysed outcomes.

Figure 3

Forest plot of the meta-analysis for the third trimester HbA_{1c} level in pregnant women with T1DM receiving CSII vs MDI therapy.

Assessing a risk of publication bias

No sign of publication bias according to the Egger's test and the Begg-Mazumdar statistic was demonstrated

towards the HbA_{1c} level, insulin dose in each trimester, risk of hypoglycaemia, risk of DKA, as well as most maternal and foetal complications, except for preeclampsia and preterm delivery.

Figure 4
Forest plot of the meta-analysis for gestational weight gain in pregnant women with T1DM receiving CSII vs MDI therapy.

Discussion

Main findings and comparison with existing literature

This meta-analysis, based on a systematic review comparing CSII and MDI therapy in pregnant women with T1DM, included for the first time, all available studies on the subject, regardless of their methodology (RCT or observational study). These broad inclusion criteria allowed us to analyse 47 publications, encompassing 7824 pregnancies complicated by T1DM, far more than earlier meta-analyses restricted only to RCTs. Our pooled results of all eligible studies showed that the HbA1c level, the main glycaemic control outcome, was slightly lower in patients using insulin pumps than MDI therapy throughout the first and second trimester of pregnancy. We also identified a few other differences in clinical maternal or neonatal outcomes.

The largest difference in the HbA1c level occurred during the first trimester, where it was almost 0.5% lower in the CSII group compared to the MDI group, and then showed a narrower difference in subsequent trimesters. In the third trimester, the difference was not significant, at a magnitude of less than 0.1%, without clinical relevance. A number of RCTs and several meta-analyses, as well as observational studies, have previously shown that CSII results in better glycaemic control than MDI in the general

T1DM population (12, 67, 68, 69, 70). It is likely that the differences favouring CSII in the current report, particularly in the first trimester, reflect the fact that women on insulin pumps had lower glucose levels already outside of pregnancy in the preconception period (69, 70). This notion is further supported by our subgroup meta-analysis that showed a larger difference in first trimester HbA1c levels in relation to the MDI group in women who started pump therapy before pregnancy, compared to women who switched to CSII at the beginning of pregnancy.

Since the individual studies included in this meta-analysis provided rather scarce information regarding patients' characteristics and the details of the interventions, a meta-regression to determine any possible associated factors was not possible. However, available data suggest that preconception care, including pregnancy planning, might have influenced the final results. In most studies presenting detailed information, the percentage of women with preconception care was higher in the CSII group than in the MDI group, while in the remaining studies, a non-significant deviation favouring pump therapy was observed. It thus seems possible that the advantage of CSII over MDI therapy might, at least partially, originate from the group construction and patients' involvement in preconception care. It is indeed well-known that diabetes care during pregnancy planning is one of the most important factors

Figure 5
Forest plot of the meta-analysis for the risk of infants being born large-for-gestational-age to pregnant women with T1DM receiving CSII vs MDI therapy.

contributing to metabolic control and obstetrical outcomes in pregnant women with T1DM, and substantially affects the HbA_{1c} level in the first trimester (71).

In our meta-analysis, the difference in HbA_{1c} values between the two arms decreased in the second trimester, and finally disappeared in the last trimester. This may be

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explained by the fact that in the clinical setting, patients on MDI therapy often participate less frequently in preconception care and pregnancy planning, but then substantially increase their awareness of the importance of optimal glycaemic control for foetal well-being as their pregnancy progresses. Subsequently, some non-random factors, such as preconception care and pregnancy planning, become less important in later months. In our study, by the end of the pregnancy, the difference between CSII and MDI therapy vanished, suggesting that both methods of insulin delivery have equal potential to achieve a target HbA_{1c} value for pregnancy, especially when the patient is highly motivated, as is typical for expecting women. One may postulate that outside pregnancy, when the level of motivation is lower, CSII therapy is associated with a slightly higher effectiveness. Interestingly, it was shown in our earlier observational study that post-pregnancy glycaemic control in women with T1DM was better in women on pumps, although it was still worse than that achieved during pregnancy (2). Furthermore, 1 study included in the meta-analysis reported that the HbA_{1c} level in the MDI group was even lower than that in the CSII arm at the end of pregnancy, although the inverse relationship was present at the beginning of the pregnancy (35).

Our meta-analysis revealed that in all 3 trimesters of pregnancy, the requirement for insulin was lower in the CSII group than in patients receiving MDI therapy. However, for unclear reasons, a high level of heterogeneity between the studies was observed. Nevertheless, the obtained results are in agreement with observations from the general population with T1DM, where pump therapy was associated with lower doses of insulin. For example, in a registry of the Slovenian population, switching from MDI to CSII therapy, led to reduction in the HbA_{1c} level and concomitant decrease in insulin requirements (70). Similar results were obtained in the prospective study on 153 patients with T1DM in whom MDI therapy was replaced by CSII, resulting in better glycaemic control and reduction of daily insulin requirements (68).

Our initial analysis did not find any difference between the two therapy modes in terms of GWG; however, some heterogeneity between the studies was observed. This was probably derived from one Spanish study reporting a higher GWG in MDI than in CSII (35), whereas the opposite tendency was observed in the remainder. In the Spanish study, the preconception HbA_{1c} level was higher in the MDI group than in the CSII group (7.6% vs 6.6%), while a reverse tendency was noticed in the third trimester (5.9% vs 6.2%). As a

result, the reduction in HbA_{1c} levels during pregnancy was much larger in patients with T1DM on MDI therapy compared to CSII. Such a substantial HbA_{1c} level reduction was associated with a higher insulin dosage, which was clearly seen in the 12th gestational week (0.70 vs 0.51 U/kg) and, at least in part, could have accounted for a higher GWG in the MDI arm. After excluding this study, a sensitivity analysis revealed a greater GWG in women with T1DM on pumps. This phenomenon might be explained by less stringent dietary habits during pump therapy, which could lead to a higher calorie intake and, thus, a larger pregnancy weight gain, as discussed in some individual studies (2, 72).

Another key outcome analysed in the current research was the number of hypoglycaemic episodes. The risk of hypoglycaemia in pregnant women with T1DM was previously reported to be 3–5 times higher in the first trimester than in the preconception period (73). The meta-analysis performed in the general T1DM population showed that CSII therapy was associated with a 3–4 times lower rate of severe hypoglycaemia (12). Somewhat unexpectedly, we found in our meta-analysis that the percentage of women who experienced at least 1 severe hypoglycaemic episode was similar in both treatment groups. There are several possible explanations for this finding, such as the different target populations (pregnant women with T1DM vs the general population with T1DM) and the different therapeutic glycaemic aims. Additionally, pregnant women on MDI less frequently received preconception care and booked antenatal appointments later in their pregnancy; thus, some hypoglycaemic episodes might have been missed, especially as most occur in the first trimester (71, 73).

The pregnancy period in women with T1DM has been linked earlier with a higher risk of not only hypoglycaemia, but also the life-threatening condition of DKA (74). Earlier data from the general population suggested a higher frequency of DKA in T1DM patients on insulin pumps (75). This was explained by the specificity of delivery method (i.e. lack of subcutaneous depot) and type of insulin use (i.e. almost exclusively short-acting analogues rather than human insulin). Indeed, even a short-term pause in insulin delivery, if not quickly discovered and eliminated, might lead to a fast rise in glycaemia and DKA occurrence. However, more recent data did not confirm this finding in the general population with T1DM (68), which is likely attributed to the technological advancement of the pumps, as well as improved patient qualification for this type of therapy (76). Our meta-analysis indeed showed that the risk of DKA was not different between the groups.

While the pooled results of 5 RCT studies published between 1986 and 1993 revealed a higher prevalence of DKA in women with T1DM on CSII therapy (7%) than on MDI therapy (0%), this difference was not statistically significant (16). In addition, observational studies published between 2010 and 2014 showed a similar risk of DKA in pregnant women with T1DM regardless of the insulin delivery method they used (25, 28, 30, 38). This seems to confirm the assumption that patient education and technological progress has reduced the risk of DKA during T1DM-complicated pregnancy observed earlier on pump therapy.

Our results suggest that insulin pump use was associated with an increased risk of infants being born LGA. This was observed in spite of the fact that the third trimester HbA1c level, a strong influential factor on the birth weight of infants born to mothers with T1DM, was almost identical in both study groups (77). One possible explanation is a higher GWG in women with T1DM on CSII therapy, since several recent reports presented an excess of maternal weight gain during pregnancy as a risk factor for neonatal macrosomia (78, 79). Additionally, it can be postulated that better glycaemic control in the first trimester might lead to a better functioning placenta later during pregnancy. This phenomenon may explain why there remains a high proportion of macrosomia reported in infants born to pregnant women with T1DM, in spite of improvement in glycaemic control that is observed in many studies (77, 80, 81). This may also possibly explain a lower risk of infants being born SGA in the CSII therapy group in this meta-analysis. Finally, the finding of a higher risk of spontaneous abortion in women on CSII therapy compared to those on MDI therapy requires comment. It seems to be a finding very likely influenced by non-random factors, mainly the more frequent pregnancy planning in the pump group. As a result, women on CSII therapy tend to book their first pregnancy appointment earlier, which may result in more frequent recording of spontaneous miscarriages (82).

Limitations

Our study has some shortcomings that may potentially influence its results. Firstly, only a few RCTs were available, having been performed many years ago and having included a small number of women; therefore, the results of our meta-analysis are derived mainly from observational studies, which have their obvious limitations. Moreover,

only 5 non-RCT publications controlled for confounding factors during the assignment process, and in most cases, data were analysed retrospectively. Therefore, the results of our meta-analysis reflect a therapeutic effect observed in the clinical setting, and the direct comparison between CSII and MDI therapy should be interpreted in the context of the methodological limitations of the available research data. Finally, we were able to include only very limited data on the most recent insulin pumps, particularly those that feature tools to integrate CSII and continuous glucose monitoring systems (CGMS), such as the low glucose suspend function, which is growing rapidly in use worldwide.

Conclusions and implications

In summary, the results of our systematic review and meta-analysis of RCTs and observational studies showed that in pregnancy complicated by T1DM, insulin pump therapy compared to MDI therapy resulted in better glycaemic control in the first trimester. However, this difference steeply decreased throughout pregnancy, probably due to its non-random origin, such as preconception care. CSII therapy was also associated with lower insulin requirements and larger weight gain in mothers, as well as an increased risk of infants being born LGA and decreased risk of being born SGA.

As both CSII and MDI therapy seem to exhibit similar potential in achieving glycaemic control in pregnant women with T1DM, the decision of choosing of either therapy should involve, among other factors, patient preferences, clinician experience, local clinical practice, as well as country-specific reimbursement policies. A special emphasis should be placed on the pregnancy planning, as well as education involving recommended diabetic diets and GWG, with the latter being particularly pertinent in patients on CSII therapy. Future studies will be needed to determine whether the newest generations of insulin pumps with integrated CGMS and elements of closed-loop monitoring systems will exhibit an advantage over the traditional MDI therapeutic approach for the management of pregnant women with T1DM.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-17-0804>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

P R, M T M: study design, protocol development; P R, A L S: searching medical databases; P R, A L S: data analysis; P R, A L S, K C, M T M: research data, data interpretation; P R, A L S, M T M: writing the manuscript; K C: critical review of the manuscript; M T M: project coordination, final approval of the manuscript. M T M is the guarantor of the data and, as such, had full access to all 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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