Insulin pump therapy would be favored by pregnant women with diabetes

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Cogent Psychology (2020), 7: 1801221
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Abstract: To evaluate retrospectively the satisfaction of continuous subcutaneous insulin infusion (CSII) compared to multiple daily infusions in Japanese women with diabetes mellitus (DM) during pregnancy, we examined 27 women with type 1 (n = 20) or type 2 (n = 6) diabetes mellitus or gestational diabetes (n = 1) who previously used CSII. Among these patients, 19 had used CSII during pregnancy, which accounted for 30 births. Questionnaires were retrospectively administered. The mean age of patients was 36.5 ± 7.0 years. The average birth weight was 3.1 ± 0.6 kg, with 62% of babies exhibiting complications. The satisfaction level of CSII for patients during pregnancy was 3.95 ± 0.26, whereas it was 1.84 ± 0.26 for multiple daily infusions (P < 0.001). CSII was generally viewed favorably by women with diabetes mellitus for glycemic management during pregnancy.

Subjects: Endocrinology; Diabetes; Obstetrics, Gynecology & Women; s Health

Key words: Continuous subcutaneous insulin infusion; multiple daily insulin injection; glycemic control; pregnancy

ABOUT THE AUTHOR

Our group of physicians and obstetricians treat many high-risk pregnant women, including for both type 1 and type 2 diabetes, and often introduce CSII to them for strict glycemic control. We find that CSII has many benefits for patients in terms of overall glycemic control and glucose variability since we can set basal insulin levels to avoid hypoglycemia and use multiple fine-tunings of bolus insulin to avoid hyperglycemia by using CSII. However, we cannot know the psychological aspects of patient satisfaction. Indeed, there are few reports showing pregnant patients' preference for CSII. As patient satisfaction is important, as are treatment outcomes for pregnant women with diabetes, we decided to survey retrospectively to identify their preferences.

PUBLIC INTEREST STATEMENT

Continuous subcutaneous insulin infusion (CSII) is the main treatment option for diabetes mellitus (DM), and reports examining the psychological aspects of using CSII are gradually increasing. Moreover, the usage of CSII during pregnancy is gradually increasing and its benefits for perinatal outcomes have been discussed. However, no studies have examined the preference for CSII therapy especially during pregnancy so far. As such, we retrospectively surveyed pregnant women to identify their preferences, as well as perinatal outcomes for CSII and multiple daily infusions (MDIs). We found that there were almost no differences in the perinatal outcomes between the MDI and CSII groups. However, overall satisfaction of glycemic control during pregnancy was significantly greater with the CSII vs. MDI group. Although there remain certain issues with CSII, it was generally considered favorable when reviewed by pregnant women with DM.
1. Introduction
The prevalence of DM (including type 1, type 2, and gestational) in pregnant women and the number of women with pre-gestational type 1 and type 2 DM is increasing, as is the number of women of reproductive age with obesity (Baran, 2019; Mathers & Loncar, 2006; Schaefer-Graf et al., 2018). Due to the detrimental consequences of hyperglycemia during pregnancy, very strict guidelines have been established to prevent maternal and fetal complications (Edited by Japan Diabetes Society, 2016–2017). While insulin therapy is frequently required and often preferred for DM in pregnant women since insulin does not traverse the placenta in pregnancy, prevention of hyperglycemia and hypoglycemia in these patients remains a challenge.

Continuous subcutaneous insulin infusion (CSII) and sensor-augmented pump (SAP) therapy are one of the insulin therapy options and the number of reports has increased that those therapies could reduce hyperglycemia without increasing hypoglycemia for patients with diabetes (Bruttomesso et al., 2008; DeVries et al., 2002; Hanaire-Broutin et al., 2000; Hoogma et al., 2006; Pickup et al., 2017; Pickup & Sutton, 2008). Many reports present the efficacy of treatments like glycemic control and perinatal outcome of CSII for pregnant women with diabetes (Abell et al., 2017; Ranasinghe et al., 2015; Weissberg-Benchell et al., 2003); however, few reports documented the patients’ emotional aspects like satisfaction levels for CSII during pregnancy. Since the outcomes of CSII during pregnancy are still controversial (Abell et al., 2017; Ranasinghe et al., 2015; Weissberg-Benchell et al., 2003) it seems to be very important to raise up the arguments as if CSII could be preferable enough to improve the quality of life and be one of the therapy options for women with diabetes especially during pregnancy.

As such, we first examined perinatal outcomes for CSII and MDIs. Next, we retrospectively surveyed the satisfaction levels of pregnant women using CSII. With those data, we would like to discuss whether CSII could be the one of the therapy options for women with diabetes especially during pregnancy regardless the perinatal outcomes.

2. Methods

2.1. Ethics statement
This study was approved by the Gunma University Institutional Review Board (ID 160102) and was performed in accordance with the ethical standards of the Declaration of Helsinki. Patients provided written informed consent before undergoing any study-related procedures.

2.2. Subjects
We reviewed the records of all women with DM that used CSII and visited the Department of Endocrinology and Diabetes, Gunma University Hospital from October to December 2016. Women without a history of delivery or DM during pregnancy were excluded. The characteristics of the study participants are presented in Table 1.

2.3. Perinatal outcome
Various perinatal outcomes were examined, as listed in Table 2. Preterm delivery was defined as a delivery at ≤37 weeks of gestation. Neonatal hypoglycemia was defined as the requirement for a glucose injection. Neonatal jaundice was defined as the requirement of phototherapy. There was one case of intrauterine fetal death; the patient was classified for admission to newborn intensive care unit (NICU) for neonatal asphyxia.
2.4. Questionnaire
We administered a questionnaire that included the following questions:

(1) What is your overall satisfaction rate for treatment during pregnancy? (Responses: 1 – greatly dissatisfied, 2 – somewhat dissatisfied, 3 – neither, 4 – slightly satisfied, 5 – very satisfied)

(2) Do you feel it was hard to manage hyperglycemia? (1 – greatly dissatisfied, 2 – somewhat dissatisfied, 3 – neither, 4 – slightly satisfied, 5 – very satisfied)

(3) Do you feel it was hard to manage hypoglycemia? (1 – greatly dissatisfied, 2 – somewhat dissatisfied, 3 – neither, 4 – slightly satisfied, 5 – very satisfied)

(4) How many calories do you feel that you consumed during the pregnancy? (1 – too little, 5 – too much)

(5) How much insulin do you feel was injected during pregnancy? (1 – too little, 5 – too much)

(6) Which treatment do you feel was superior during pregnancy? (MDI, CSII, or Not Sure)

(7) Which treatment are you willing to use for next pregnancy? (MDI, CSII, or Not Sure)

(8) Which treatment are you willing to recommend to your friends? (MDI, CSII, or Not Sure)

(9) Please state any problems encountered with CSII during pregnancy/non-pregnancy. (an open-ended question).

2.5. Statistical analysis
All results are expressed as mean±SD for continuous variables and as absolute numbers and relative percentages for categorical variables. All continuous variables were non-normally distributed, and the group comparisons were performed with the Wilcoxon rank-sum test for non-normally distributed data for continuous variables. The Pearson’s chi-squared test was used for categorical variables. All
tests for significance and the resulting P values were two-sided, with a level of significance of 5%. Statistical analyses were performed using JMP 9 (SAS Institute Inc., Cary, NC).

### 3. Results

Among the 27 women with DM, 20 (74.1%) had type 1 and 2 (22.2%) had type 2; 1 patient (3.7%) had gestational diabetes. Their profiles are presented in Table 1. CSII was administered in 22 out of 30 pregnancies (CSII group). The remaining pregnancies were classified as the MDI group. There were four patients treated with MDI in their preceding pregnancy and CSII in their subsequent pregnancy. One patient switched from MDI to CSII and back to MDI during the course of the first pregnancy. In addition, there were two women that did not need insulin following delivery. There were six women who discontinued CSII treatment following delivery and four who changed their treatment from CSII to MDI.

Perinatal outcomes are presented in Table 2. Only birth asphyxia was statistically different between the CSII and MDI groups (P = 0.037). There were no significant differences between the two groups for all remaining perinatal outcomes (Table 2) including the choice of cesarean delivery (Supplementary Figure).

While the perinatal outcomes were limited difference between groups, patients had significantly different feelings based on the provided questionnaire (Table 3). Overall satisfaction level of

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### Table 2. Perinatal status of participants and their infants

|                      | All   | MDI   | CSII  | p-value |
|----------------------|-------|-------|-------|---------|
| N                    | 30    | 8     | 22    |         |
| Gestational age at delivery (week) | 37.7 ± 2.6 | 37.7 ± 0.7 | 37.8 ± 0.5 | 0.847   |
| Pregnancy hypertension (%) | 13    | 0     | 18.2  | 0.195   |
| Delivery type         |       |       |       |         |
| Vaginal delivery (%)  | 59    | 80    | 53    | 0.279   |
| Caesarean section (%) | 41    | 20    | 47    | 0.343   |
| Preterm delivery (%)  | 13    | 13    | 14    | 0.935   |
| Birth weight (kg)     | 3.08 ± 0.6 | 3.29 ± 0.2 | 2.99 ± 0.1 | 0.233   |
| AFD (%)               | 63    | 38    | 69    | 0.129   |
| SFD (%)               | 7     | 13    | 5     | 0.440   |
| HFD (%)               | 30    | 38    | 32    | 0.770   |
| Any complications (%) | 63    | 63    | 63    | 0.954   |
| NICU admission (%)    | 37    | 38    | 37    | 0.095   |
| Neonatal jaundice (%) | 17    | 14    | 18    | 0.812   |
| Neonatal hypoglycemia (%) | 21  | 14    | 23    | 0.631   |
| Birth asphyxia (%)    | 23    | 50    | 14    | 0.037   |
| Respiratory distress (%) | 20  | 13    | 23    | 0.536   |
| Malformation (%)      | 4     | 0     | 5     | 0.566   |

AFD: appropriate for dates infant, SFD: small for dates infant, HFD: heavy for dates infant
glycemic control during pregnancy was significantly different between the MDI and CSII groups (P < 0.001). The perceived difficulty of managing hyperglycemia during pregnancy was not statistically different between the MDI and CSII groups (P = 0.413). However, the perceived difficulty of managing hyperglycemia was marginally greater in the MDI vs. CSII group (P = 0.064). In contrast, there was no significant difference in women that perceived the optimal amount of food consumed or insulin dose administered between the two groups, which indicate patients believed they could manage these variables regardless of the method.

Based on questions indicating overall satisfaction levels (Table 4), 79% of women treated with CSII felt that CSII was superior to MDI (5%). None of women with MDI felt that MDI during pregnancy was better than CSII. Most women with CSII (90%) wanted to use CSII in their next pregnancy and, surprisingly, all the women with MDI wanted to manage their next pregnancy with CSII. Moreover, 84% of the CSII group and 100% of the MDI group would recommend CSII as the preferred method to a friend with DM. These data collectively indicated patients far prefer CSII as the ideal therapy during pregnancy, even when perinatal outcomes were of limited difference.

During open discussion of the potential benefits and issues of CSII during pregnancy and non-pregnancy, patients perceived fewer problems as compared to medical costs, the insulin pump, treatment obstacles, and difficulty in pregnancy vs. non-pregnancy (Table 5) indicating that women tended to be more motivated for glycemic control and could ignore some problems more during pregnancy. The following responses in the free description field were provided: 1) insulin could be injected before every meal, but not with an insulin pen; 2) CSII is preferable during emesis gravidarum; 3) insulin could be injected in smaller increments with CSII; 4) the amount of insulin can be calculated with the bolus calculator with CSII, whereas manual calculations are required with the insulin pen; and 5) the management of blood glucose was easier with CSII. These reasons are why women felt CSII was a better treatment than MDI during pregnancy.
This retrospective study demonstrated a greater satisfaction level with CSII during pregnancy, as well as a greater willingness to use it for future pregnancies with limited perinatal outcomes. To our best knowledge, this is the first report demonstrating the psychological aspect of CSII for women with diabetes during pregnancy.

Perinatal outcomes were very limited in this study. Indeed, previous meta-analyses reported that perinatal outcomes were not significantly different between MDI and CSII (Abell et al., 2017; Ranasinghe et al., 2015; Weissberg-Benchell et al., 2003). However, such differences cannot be

### Table 4. Questionnaires regarding treatment for next pregnancy

|                      | All    | CSII   | MDI    |
|----------------------|--------|--------|--------|
| Which treatment do you feel was superior during pregnancy? |  |        |        |
| CSII (%)             | 69     | 79     | 43     |
| MDI (%)              | 4      | 5      | 0      |
| Not Sure (%)         | 27     | 16     | 57     |
| Which treatment are you willing to use for next pregnancy? |  |        |        |
| CSII (%)             | 92     | 90     | 100    |
| MDI (%)              | 4      | 5      | 0      |
| Not Sure (%)         | 4      | 5      | 0      |
| Which treatment are you willing to recommend to your friends? |  |        |        |
| CSII (%)             | 88     | 84     | 0      |
| MDI (%)              | 12     | 100    | 16     |

MDI: multiple daily infusion, CSII: continuous subcutaneous insulin infusion

### Table 5. Problems with CSII during pregnancy/non-pregnancy (open-ended question)

|                          | Non-pregnancy | During pregnancy |
|--------------------------|---------------|------------------|
| Medical cost (%)         | 85            | 44               |
| Skin problems (%)        | 59            | 59               |
| Pump trouble (%)         | 48            | 22               |
| Feeling an obstacle (%)  | 48            | 30               |
| Anxiety (%)              | 19            | 19               |
| Troublesome insertion of infusion sets of CSII (%) | 15 | 22 |
| Too much material for infusion sets of CSII (%) | 11 | 0 |
| Difficulty in dressing (%) | 11           | 0                |
| Discomfort during bolus injection (%) | 4            | 0                |

CSII: continuous subcutaneous insulin infusion

4. Discussion

This retrospective study demonstrated a greater satisfaction level with CSII during pregnancy, as well as a greater willingness to use it for future pregnancies with limited perinatal outcomes. To our best knowledge, this is the first report demonstrating the psychological aspect of CSII for women with diabetes during pregnancy.
concluded without addressing the biases in these reports. In this study, perinatal outcomes were relatively the same between these groups; however, the MDI group had a relatively larger rate of birth asphyxia compared with the CSII group. Following inspection of the data, it was revealed that information obtained from the MDI group was earlier. Thus, the observed differences might reflect progress in the field of glycemic control and parturition management.

Despite limited perinatal outcomes patients in this study tended to prefer CSII vs. MDI, regardless of current treatment. The type of diabetes did not affect which treatment was preferred, either. More importantly, women in the MDI group preferred CSII to their current treatment. The percent of women in the MDI group choosing “unknown” in the MDI group might be due to an awareness of CSII therapy for glucose management during pregnancy.

There could be several reasons why pregnant women with DM preferred CSII therapy. First, the collected data on self-evaluation of glycemic control indicated that hypoglycemia was easy to manage during pregnancy for our CSII group, as recently reported that the incidence of hypoglycemia was decreased with CSII compared to MDI during pregnancy (Ranasinghe et al., 2015). While pregnant women with DM tend to be more concerned about hyperglycemia than hypoglycemia (Langer & Langer, 1994), the difficulty reported in the management of hypoglycemia might be overridden by the easier management of hyperglycemia during pregnancy. Women with DM find it easier to manage hyperglycemia with CSII, which may reflect a lower psychological hurdle of insulin injection with CSII. Moreover, the adjustment of insulin dose with CSII is slightly easier, as insulin can be injected in increments of 0.1 units in our study. More importantly, management of glycemic control in pregnant women with DM can be assessed through measurement of HbA1c level, as well as fluctuations in blood glucose concentration (Dalfra et al., 2010). In this study, patients reported that CSII effectively suppressed glycemic fluctuations primarily through the prevention of hyperglycemia. Indeed, several papers reported a statistically significant reduction in glucose variability for patients using CSII pumps compared to those using MDI (Bruttomesso et al., 2008; DeVries et al., 2002; Hanaire-Broutin et al., 2000; Hoogma et al., 2006). More importantly, it has been reported that there is an improved quality of life for non-pregnant patients using CSII pumps because of not only overall glycemic control but also less glucose variability (Bruttomesso et al., 2008; DeVries et al., 2002; Hanaire-Broutin et al., 2000; Hoogma et al., 2006). These reasons also might explain the overall patient satisfaction with CSII also during pregnancy.

Several issues have been raised regarding CSII therapy including medical cost, skin trouble, and diabetic ketoacidosis related to mechanical issues with pump (Blair et al., 2019; Pickup, 2012). All of these risks can have serious consequences on the outcome of pregnancy (Mukhopadhyay et al., 2007). In this study, we investigated if women with DM feel differently about the problems accompanied by CSII. Anxiety and trouble with insertion of infusion sets were problems that occurred during both pregnancy and non-pregnancy. However, the women felt that medical cost and treatment obstacles were less of an issue during pregnancy. Importantly, they felt that the amount of pump trouble decreased during pregnancy, indicating that they carefully managed CSII to avoid hyperglycemia or even ketoacidosis due to pump trouble during pregnancy.

In this study, four patients who underwent CSII therapy during pregnancy stopped using it despite the need for insulin therapy after delivery. A continuation would indicate they felt more satisfied by CSII, similar to that previously reported for pregnant women, who tended to continue insulin therapy after delivery for its convenience (Gabbe et al., 2000). Although there were various reasons for changing the device, medical costs were a problem for all patients as reported before (Blair et al., 2019; Pickup, 2012). Furthermore, more than half of the women with diabetes referred to medical expenses and skin trouble as the chief problem in the use of CSII in both non-pregnancy
and pregnancy states. DM is a medical condition that requires long-term management and addressing these issues is essential for the improvement and continuation of CSII therapy.

5. Conclusions
Several limitations to this study that must be addressed: First, it had a cross-sectional retrospective design, with patients recruited from a single center. The number of participants is small, especially in gestational diabetes. Thus, patient characteristics and/or treatment may vary depending on location. A multicenter study will be required to address this limitation. Additionally, CSII and SAP therapies are not so popular during pregnancy in Japan. Therefore, it is essential to accumulate cases that may support and expand upon our findings.

In summary, overall satisfaction during pregnancy was significantly greater with the CSII than that with MDI, while there were almost no differences in the perinatal outcomes between the MDI and CSII groups. Since outcomes of CSII during pregnancy have been not confirmed, these data could help physicians and patients choose CSII during pregnancy as one of the treatment options. Future studies are needed using larger cohorts to confirm these results.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria or authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.
Competing interest: The authors declare no competing interest.

Supplementary material
The supplemental data for this article can be accessed here.

Cover Image
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Citation information
Cite this article as: Insulin pump therapy would be favored by pregnant women with diabetes, Aya Osaki, Eijiro Yamada, Yasuyo Nakajima, Yuko Kasa, Yoko Shimoda, Akiko Taki, Kazuhiro Horiguchi, Satoshi Yoshino, Maki Inoue, Tsugumichi Saito, Takashi Kameda, Shuichi Okada & Masaanbu Yamada, Cogent Psychology (2020), 7: 1801221.

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