Type 1 diabetes control and pregnancy outcomes in women treated with
continuous subcutaneous insulin infusion (CSII) or with insulin glargine and
multiple daily injections of rapid-acting insulin analogues (glargine–MDI)

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Received 28 November 2010; received in revised form 1st February 2011; accepted 2 February 2011
Available online 6 April 2011

Abstract

Aim. – The best way to treat pregnant patients who have type 1 diabetes is still unclear. For this reason, the present study compared metabolic control and maternal–fetal outcomes in patients treated with continuous subcutaneous infusions of rapid-acting insulin analogues (CSII) or with insulin glargine and multiple daily injections of rapid-acting insulin analogues (glargine–MDI).

Methods. – This retrospective multicentre study involved 144 women with type 1 diabetes, 100 of whom were using CSII and 44 glargine–MDI. Outcomes analyzed were metabolic control, diabetes complications, pregnancy outcome, perinatal morbidity and mortality, and fetal malformations.

Results. – The two groups were comparable for age, prepregnancy BMI, primiparous rate and diabetes complications, although patients using CSII had longer duration of diabetes (P = 0.03) and higher White classifications (P = 0.04). In both groups, metabolic control improved during pregnancy, but good control was reached earlier among patients using CSII. At parturition, patients using CSII had lower HbA1c (6.2 ± 0.7% vs 6.5 ± 0.8%; P = 0.02) and required less insulin (P < 0.01). Weight gain was similar in both groups, and maternal–fetal outcomes did not differ.

Conclusion. – In pregnant patients with type 1 diabetes, MDI and CSII are equivalent in terms of metabolic control and fetal–maternal outcomes, although patients using CSII achieved good control earlier and with less insulin.

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Keywords: Type 1 diabetes; Pregnancy; Continuous subcutaneous insulin infusion; Multiple daily injections; Glargine

Résumé

Contrôle du diabète et évolution de la grossesse chez des diabétiques de type 1 traitées par perfusion sous-cutanée continue d’insuline (CSII) ou par injections multiples d’un analogue rapide de l’insuline et d’insuline glargine.

Objectif. – Comparer le contrôle glycémique et le pronostic fœtomaternel chez des diabétiques de type 1, traitées par administration sous-cutanée continue d’insuline (CSII) ou par injections multiples d’un analogue rapide de l’insuline et insulin glargine (Glargine-MDI).
Méthodes. – Étude rétrospective, multicentrique menée chez 144 femmes diabétiques de type 1, 100 traitées par CSII et 44 par glargine-MDI. Les paramètres analysés étaient le contrôle métabolique, les complications du diabète, l’évolution de la grossesse, la morbidité, la mortalité et les malformations fœtales.

Résultats. – Les deux groupes étaient semblables pour ce qui concerne âge, BMI pré grossesse, nombre de primipares et complications du diabète, mais les patientes sous CSII avaient des taux de HbA1c inférieurs (6,2 ± 0,7 vs 6,5 ± 0,8 % ; P = 0,02), ainsi que des besoins insuliniques plus faibles. La prise de poids était identique dans les deux groupes. Les données fœtomaternelles étaient identiques dans les deux groupes indépendamment du type de traitement.

Conclusion. – Chez les femmes enceintes diabétiques de type 1, la glargine-MDI et la CSII sont équivalentes pour le contrôle métabolique et mère-fœtus, mais les patientes sous CSII obtiennent un contrôle satisfaisant plus précocement, avec de plus faibles doses d’insuline.
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Mots clés : Diabète de type 1 ; Grossesse ; Infusion sous-cutanée continue d’insuline ; Injections multiples d’insuline ; Glargine

1. Introduction

In women with type 1 diabetes mellitus (T1DM), pregnancy is associated with increased risk of congenital malformations, obstetric complications, and perinatal morbidity and mortality of conceptus. As high blood glucose levels are important in the pathogenesis of complications during pregnancy in patients with diabetes, the goal of treatment is to obtain blood glucose values as close to normal as possible during pregnancy and at the time of conception. In patients with diabetes, continuous subcutaneous insulin infusion (CSII) has proved better than multiple daily injections (MDI) in reducing HbA1c and hypoglycaemic episodes [1,2]. Yet, whether or not this holds true during pregnancy remains unclear, as patients with T1DM treated with CSII could be at increased risk of maternal diabetic ketoacidosis (DKA) and neonatal hypoglycaemia [3].

Insulin glargine (IG) is a long-acting insulin analogue with a flatter action profile, longer duration of action and more reproducible effects on blood glucose levels compared with neutral protamine Hagedorn (NPH) insulin. Studies involving non-pregnant patients indicate that the use of IG is associated with fewer episodes of nocturnal hypoglycaemia and equal or better glycaemic control than with NPH. Therefore, IG could have a special indication during pregnancy.

Thus far, retrospective studies have shown that the use of IG in pregnant patients is associated with a comparable or lower incidence of congenital malformations compared with other types of insulin [4–13]. Furthermore, it has been shown that IG, when used at therapeutic concentrations, does not cross the placenta [14]. However, because there is only limited evidence regarding safety, IG is not accepted as a routine treatment of diabetes and pregnancy in the European countries.

As studies comparing CSII and MDI based on IG are lacking, the objective of the present multicentre investigation was to retrospectively compare metabolic control and maternal–fetal outcomes in pregnant women with T1DM who were intensively treated from the time of conception with either CSII, based on rapid-acting insulin analogues, or MDI, based on rapid-acting insulin analogues and IG.

2. Patients and methods

2.1. Patients

A total of 469 consecutive pregnant women with T1DM, followed from 2001 to 2009 at 10 Italian centres (Bergamo, Chieti, Messina, Milano, Padova [two clinics], Perugia, Pisa, Ravenna and Udine), were retrospectively evaluated. Excluded from the study were 276 patients being treated with MDI based on NPH, and 49 patients being treated with CSII that started during pregnancy. For the present investigation, 144 patients were recruited. Of these, 44 were being treated with MDI, using rapid-acting insulin analogues (either aspart or lispro) and glargine (glargine–MDI), while 100 were being treated with CSII based on either aspart or lispro (CSII). Patients in both groups had started their respective glargine–MDI and CSII treatments at least six months before conception. Indeed, all patients started CSII before pregnancy because they could not achieve acceptable metabolic control with MDI based on NPH (61%) or glargine (39%). All of the women knew that glargine was unlicensed for use during pregnancy, and all of them were followed-up by the same centre throughout their entire pregnancy. No patient had significant endogenous insulin secretion (fasting C-peptide < 0.2 nmol/L).

2.2. Data collection

Maternal characteristics of interest included body mass index (BMI), age at conception and number of pregnancies, duration of diabetes at conception, microvascular complications at conception (retinopathy, nephropathy), blood pressure before pregnancy, White classification, type of insulin used, insulin requirement, HbA1c, and body weight before pregnancy and every three months thereafter.

As for maternal–fetal outcomes, these included the number of ketoacidoses or severe hypoglycaemias, gestational hypertension, preeclampsia, cholestasis, new or progression of retinopathy and nephropathy in the mothers-to-be. In the fetuses, abortion, perinatal mortality, gestational age at birth, preterm
labour, vaginal/caesarean delivery, birth weight, skull circumference, weight percentile, “large for gestational age” (LGA) or “small for gestational age” (SGA), macrosomia, APGAR score at 1 and 5 min after birth, shoulder dystocia, hypoglycaemia, hyperbilirubinaemia, need for intensive care, respiratory distress and malformations were evaluated.

Ketoacidosis was defined as hyperglycaemia and ketonaemia with arterial pH less or equal to 7.3. Severe hypoglycaemia in the mother was defined as events requiring the assistance of another person. Retinopathy was classified as absent, low grade, moderate, proliferative and treated with a laser. Nephropathy was defined as daily excretion of albumin greater or equal to 30 mg/24 h and/or as serum creatinine above the normal limit. Hypertension was defined as a systolic blood pressure greater than 140 mmHg and/or diastolic pressure greater or equal to 90 mmHg, or the use of antihypertensive drugs before becoming pregnant. Preeclampsia was defined as gravidic hypertension and proteinuria greater or equal to 300 mg/L in a 24 h urine sample after 20 weeks of gestation. Cholestasis was defined as pruritus with or without jaundice, and increased blood levels of liver enzymes and biliary salts. Abortion was defined as pregnancy interruption before week 26 of gestation. Perinatal mortality was defined as fetal death between week 28 of gestation and the first seven days of life. Preterm labour was defined as delivery before 37 + 0 weeks of gestation. Newborns were considered LGA if birth weight was greater than 90th percentile and SGA if birth weight was less than 10th percentile, based on national anthropometric standards [15]. Neonatal ponderal index (PI) was defined as the ratio of weight to length cubed (g/cm³), with a PI greater than 2.85 g/cm³ considered excessive growth [16]. Macrosomia was defined as a delivery weight greater than 4000 g. Neonatal hypoglycaemia was defined as blood glucose less than 40 mg/dL during the first 24 h of life. Hyperbilirubinaemia was defined as blood bilirubin greater than 12 mg/dL. Respiratory distress was defined as respiratory insufficiency, presenting as changes in respiratory frequency, apnoic spells, bradycardia and cyanosis. Congenital anomalies and malformations were classified according to EUROCAT [17], and fetal morbidity was classified according to obstetric quality indicators [18].

2.3. Management approach

Glucose monitoring was performed before and after meals, and at bedtime, and the insulin dose adjusted to achieve optimal control. Diet depended upon the pregestational BMI and gestational period. Visits were every two weeks until week 30 and weekly thereafter. HbA1c values were measured by high-performance liquid chromatography (HPLC; HA8121, Menarini Diagnostici, Firenze, Italy) at monthly intervals (non-diabetic range: 3.4–5.9%). Obstetric checkups were carried out according to the guidelines for obstetric management in diabetic pregnancies. Patients contacted the healthcare team by telephone if problems arose. Retinopathy was assessed at the first, second and third trimesters in patients without retinopathy, and monthly in those with the condition. Subjects with proliferative retinopathy were referred for laser treatment when necessary. Progression/new cases of retinopathy were defined as a higher stage than at baseline. Methyldopa was used to treat hypertension during pregnancy. Albumin excretion rate and serum creatinine were determined every three months. Ketoacidosis and severe hypoglycaemic episodes were registered.

2.4. Statistical analysis

The statistical analysis was carried out with SPSS statistical software (SPSS, Chicago, IL, USA). Data are presented as means ± SD. Means of independent groups were compared, using Student’s t test, after checking for normal distribution. When Levene’s test for equality of variances was significant, then Student’s t test for unequal variances was used. For analysis of paired data, Student’s t test for paired data was used. For analysis of categorical variables, the results are expressed as percentages. To compare frequencies, Pearson’s chi-square test was used or, in the case of small frequencies, Fisher’s exact test. P < 0.05 was considered significant.

3. Results

The participants’ baseline anthropometric and clinical data are presented in Table 1. The proportion of women who planned their pregnancy was 87% in the CSII group and 41% in the glargine–MDI group (P=0.023). At the time of conception, those using CSII and MDI were similar in terms of age, BMI, primiparous rate, retinopathy, nephropathy and hypertension, but the duration of diabetes was shorter among patients using glargine–MDI (P=0.03). Patients using CSII had higher White classifications (P=0.04; Table 1). Most patients were taking insulin lispro (79% for CSII, 68% for MDI). At conception, HbA1c and insulin dosages were not significantly different in the two treatment groups (Table 1). HbA1c decreased during pregnancy in both groups although, from the end of first trimester, values in the CSII group were significantly lower (Table 2). However, the net decreases in HbA1c during the pregnancy were similar: 1.03 ± 0.8% with CSII; and 1.2 ± 1.6% with glargine–MDI (not significant, NS).

During the pregnancy, the women using CSII increased their daily insulin dose by 26%, while those using glargine–MDI increased their insulin by 42%. In fact, at the time of conception, the daily insulin dose was 0.58 ± 0.18 U/kg/day among patients using CSII and 0.66 ± 0.33 U/kg/day among those using MDI (NS). At the end of pregnancy, the daily insulin dose was 0.73 ± 0.26 U/kg/day with CSII and 0.95 ± 0.35 U/kg/day with MDI (P<0.01). Interestingly, patients using MDI required more insulin at meals throughout their pregnancy (P<0.01).

Body weight changed similarly in the two groups, increasing by 13.0 ± 7.0 kg in patients using CSII and 13.4 ± 4.0 kg in those using MDI.

The number of severe hypoglycaemic or ketoacidosis episodes (data from 94 patients using CSII and 44 patients using MDI), blood pressure, preeclampsia and cholestasis (data from 93 patients using CSII and 44 patients using MDI) were also similar in the two treatment groups (Table 2). However,
Table 1
Baseline anthropometric and clinical characteristics of type 1 diabetic women treated with either continuous subcutaneous infusion of rapid-acting insulin analogues (CSII) or with insulin glargine and multiple daily injections of rapid-acting insulin analogues (glargine–MDI).

<table>
<thead>
<tr>
<th>Variable</th>
<th>CSII</th>
<th>Glargine–MDI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>100</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.0 ± 4.4</td>
<td>31.4 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>16.5 ± 7.3</td>
<td>13.5 ± 7.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.52 ± 3.22</td>
<td>23.63 ± 4.71</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%) (mmol/mol)</td>
<td>7.20 ± 0.8455</td>
<td>7.66 ± 1.6860</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin requirement (U/kg/day)</td>
<td>0.58 ± 0.18</td>
<td>0.66 ± 0.33</td>
<td>NS</td>
</tr>
<tr>
<td>Nulliparity rate</td>
<td>66 (66)</td>
<td>24 (54.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Prepregnancy hypertension</td>
<td>8 (8)</td>
<td>3 (6.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Prepregnancy retinopathy</td>
<td>37 (37)</td>
<td>11 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Prepregnancy nephropathy</td>
<td>10 (10)</td>
<td>2 (4.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Planned pregnancy</td>
<td>87 (87)</td>
<td>18 (41)</td>
<td>0.023</td>
</tr>
<tr>
<td>White classification BCD + R + RF</td>
<td>21 (21)32 (32)47 (47)</td>
<td>18 (40.9)11 (25)15 (34)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Values are presented as absolute numbers (%) or as means ± SD; NS: not significant; B: age at onset > 20 years or duration < 10 years; C: age at onset < 20 years or duration 10–19 years; D: age at onset < 10 years or duration > 20 years, background retinopathy or hypertension; R: proliferative retinopathy or vitreous bleeding; RF: proliferative retinopathy and nephropathy.

Retinopathy worsened in nine out of 93 patients (9.7%) with CSII, and in two out of 44 patients (4.6%) with MDI (NS). In both groups, retinopathy worsened mostly in patients who had higher White classification or retinopathy before pregnancy. In two out of 93 patients in the CSII group, nephropathy worsened and two developed new nephropathy, although the difference compared with MDI was not statistically significant (Table 2). Fetal outcomes were similar in both treatment groups (Table 2).

4. Discussion
The present study compared maternal–fetal outcomes of pregnant women with T1DM being treated from conception

Table 2
Maternal–fetal outcomes for pregnant type 1 diabetics treated with CSII or glargine–MDI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CSII</th>
<th>Glargine–MDI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)1st trimester2nd trimesterEnd of pregnancy</td>
<td>6.6 ± 0.7</td>
<td>7.2 ± 1.3</td>
<td>0.00055</td>
</tr>
<tr>
<td>Severe hypoglycaemic episodes</td>
<td>3 (3.2)</td>
<td>2 (4.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Ketoacidosis episodes</td>
<td>1 (1.1)</td>
<td>2 (4.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>14 (15.1)</td>
<td>3 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>9 (9.7)</td>
<td>1 (2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Progression/new cases of retinopathy</td>
<td>9 (9.7)</td>
<td>2 (4.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Progression/new cases of nephropathy</td>
<td>4 (4.3)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Fetal outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abortion</td>
<td>7 (7)</td>
<td>2 (4.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Preterm delivery (&lt; 37 weeks)</td>
<td>30 (32.3)</td>
<td>14 (34.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Cesarean delivery rate</td>
<td>72 (77.4)</td>
<td>30 (73.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>36.7 ± 2.0</td>
<td>36.6 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3390.9 ± 662.5</td>
<td>3243.2 ± 698.9</td>
<td>NS</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>46 (46)</td>
<td>20 (45.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Ponderal index &gt; 2.85 (g/cm³)</td>
<td>33 (33)</td>
<td>12 (27.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>13 (13.98)</td>
<td>6 (14.63)</td>
<td>NS</td>
</tr>
<tr>
<td>APGAR score at 1 min</td>
<td>8.5 ± 1.3</td>
<td>8.4 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>APGAR score at 5 min</td>
<td>9.5 ± 1.4</td>
<td>9.6 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>1 (1.1)</td>
<td>2 (4.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>21 (22.8)</td>
<td>8 (19.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>16 (17.4)</td>
<td>11 (26.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Need for intensive care</td>
<td>18 (19.6)</td>
<td>9 (21.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>9 (9.9)</td>
<td>4 (9.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Malformations</td>
<td>5 (5.5)</td>
<td>1 (2.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are presented as absolute numbers (%) or as means ± SD; NS: not significant.

a CSII vs glargine–MDI.
with either glargine–MDI or CSII. HbA1c levels before pregnancy were similar in the two groups, but those using CSII had a longer duration of diabetes and more chronic complications, as indicated by the distribution of White classifications. As expected, more of the women in the CSII group had planned their pregnancy, as pregnancy was one reason to start CSII [19]. During pregnancy, HbA1c improved in both groups, but those using CSII achieved low HbA1c values earlier and with smaller daily insulin doses, possibly due to better insulin pharmacokinetics with CSII [19]. Interestingly, patients using MDI needed more insulin at meals, most likely because meal boluses covered both meal carbohydrates and part of their insulin requirements between meals.

Considering maternal outcomes, in contrast to reports in the literature [3,20–23], more ketocidoses were not found among patients using CSII, possibly as a result of patient education and the tight schedule of glucose checks [21]. The rate of severe hypoglycaemic episodes was similar in both groups. Although mild hypoglycaemias were not counted, the indirect evidence suggests that these could have been fewer among patients using CSII, as they received less insulin and did not gain weight compared with those being treated with glargine–MDI.

It is accepted that the risk and progression of retinopathy during pregnancy are related to metabolic control, retinopathy status before conception and diabetes duration [24,25]. Accordingly, retinopathy worsened among women with mild/moderate retinopathy at conception and with longer diabetes duration, irrespective of the mode of insulin administration.

However, the effects of pregnancy on diabetic nephropathy have yet to be clarified. A current hypothesis is that pregnancy-associated hyperfiltration worsens nephropathy [24]. In the present study, worsening nephropathy was found only among patients using CSII, who also had a longer duration of disease and poorer baseline renal function. Intensified antihypertensive therapy might reduce adverse pregnancy outcomes in women with microalbuminuria or nephropathy [26] but, at present, there is uncertainty over what is the best strategy. Our patients received antihypertensive treatment sufficient to obtain satisfactory blood pressure levels.

Regarding fetal outcomes, no differences were observed in the two groups of patients. The high number of preterm and caesarean deliveries was mostly due to preeclampsia and LGA fetuses. The relationship between these adverse outcomes and diabetes is unclear, as the risk factors are numerous [27,28]. The number of premature deliveries was similar to those in other published reports. A recent US study showed that preterm delivery is five times more likely among diabetic women (35% vs 7% in non-diabetics) [29]. Among our present study patients, caesarean section was more frequent than in other European countries, where the prevalence is 44–58%. The discrepancy most likely reflects the fact that, in Italy, caesarean section is performed more frequently than in other European countries [28].

The present study also found a large number of LGA fetuses, which is in agreement with the recent findings of Mathiesen et al. [30], who found 3.5–4.5 times more LGA fetuses among diabetic women compared with non-diabetic pregnancies. There was, however, no difference in the number of LGA fetuses between patients treated with CSII and MDI. Also, no SGA neonates were found, a possible indication that our patients had no macrovascular complications.

Complications due to preterm delivery, such as hyperbilirubinaemia and respiratory disturbances, were similar in the two groups. Fetal malformations (3–6%) were within the expected national values (3.2–9%) [28], and were similar whether patients were treated with CSII or MDI [29].

However, the present study has some limitations, being a retrospective study in which patients were assigned to either CSII or MDI either by their own choice or their healthcare physician. Also, the glargine–MDI group was smaller in number than the CSII group, although this disproportion reflected the everyday clinical practice at the time of data collection, given that glargine has only recently been accepted for diabetes treatment during pregnancy. The present study also involved only a tiny fraction of Italian centres and, thus, may not represent the situation in the whole country. However, the size of our sample population should be sufficient to identify all serious untoward effects with frequencies greater than 1% [31].

Interestingly, in our study, women treated with CSII had longer durations of diabetes and more chronic complications of diabetes. However, this unfavourable distribution of patients did not result in poorer glucose control or obstetric outcomes compared with MDI. On the contrary, our study found that, during early pregnancy, CSII allowed better metabolic control and with a lower daily insulin dose.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A.

IGCSIIP (Italian Group for Continuous Subcutaneous Insulin Infusion in Pregnancy) investigators: Alessandro Roberto Dodesini, Roberto Trevisan (Ospedali Riuniti, Bergamo); Ester Vitalononna, Livia Cavuto (University of Chieti); Antonino Di Benedetto, Desiree Cannizzaro (University of Messina); Matteo Bonomo, Elena Meneghini, Daniela Corica (Niguarda Ca’ Granda Hospital, Milano); Daniela Bruttomesso, Silvana Costa, Michela Dal Pos, Maria Grazia Dal Frà, Annunziata Lapolla (University of Padova), Daniela Bruttomesso, Silvana Costa, Michela Dal Pos, Maria Grazia Dal Frà, Annunziata Lapolla (University of Padova), Daniela Bruttomesso, Silvana Costa, Michela Dal Pos, Maria Grazia Dal Frà, Annunziata Lapolla (University of Padova), Daniela Truscia (Padova Hospital); Elisabetta Torlone, Silvia Arnone, Giancarlo di Renzo (University of Perugia); Graziano Di Cianni, Laura Volpe (University of Pisa); Francesca Pellicano, Paolo di Bartolo (Ravenna Hospital); and Laura Tonutti (Udine Hospital).

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