Blood ketone monitoring: a comparison between gestational diabetes and non-diabetic pregnant women

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SUMMARY

Aim: To measure ketonemia in a control population of pregnant women and in a population of women with gestational diabetes (GDM). To define a normal ketonemia threshold for the controls and to determine whether or not this value could play a role in the clinical management of women with GDM.

Method: Fifty-six women with a normal OGTT and 49 women with GDM were included and monitored from the 25th to the 37th week of pregnancy. Control subjects agreed to perform glycaemia and ketonemia self-monitoring 3 times a day. In addition, women with GDM were asked to measure their postprandial glycaemia. Glycaemia and ketonemia measurements were performed using Optium™ meters. Subjects kept a 24-hour food record twice a week.

Results: The mean ketonemia was lower in the control group than in the GDM group (0.01±0.10 vs. 0.04±0.09 mmol/l; P<0.001). Ketonemia values measured before the midday meal and prior to the evening meal were lower for control subjects than for GDM patients (P=0.002 and P=0.005). Fasting ketonemia was unrelated to ketonuria in the GDM group, whereas there was a correlation in the control group (P=0.006). At least one chronic increase in ketonemia levels was observed in 47% of the women, with GDM, compared with only 12% of controls. The lowest levels of evening glycaemia correlated with the highest levels of ketonemia; women with GDM reported lower food and carbohydrate intakes than controls (P<0.001).

Conclusion: This work has enabled the establishment of ketonemia reference standards in non-diabetic pregnant women. If ketonemia does indeed indicate overly restrictive dietary behavior, this parameter could be employed for monitoring adherence to the nutritional recommendations for GDM.

Key-words: Gestational diabetes · Blood ketone monitoring · Ketonemia.


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RESUME

Suivi des concentrations plasmatiques des corps cetoniques durant la grossesse : comparaison entre diabete gestationnel et grossesse normale

Objectif: Mesurer la cétonémie de femmes enceintes avec grossesse normale et de femmes avec diabète gestationnel (GDM). Déterminer les valeurs normales de la cétonémie au cours de la grossesse et voir si ces valeurs peuvent être différentes en cas de diabète gestationnel.

Méthodes: 56 femmes avec grossesse normale et 49 avec diabète gestationnel sont incluses dans l’étude ; les femmes du groupe témoin ont accepté de mesurer leur glycémie et leur cétonémie 3 fois par jour avant chaque repas ; les femmes avec GDM ont mesuré leur glycémie 6 fois par jour et la cétonémie avant chaque repas ; glycémies et cétonémies étaient mesurées avec le même lecteur Optium™ ; la cétonurie était contrôlée le matin au réveil ; chaque femme réalisait un relevé alimentaire 2 fois par semaine.

Résultats: La cétonémie moyenne était plus basse dans le groupe témoin que dans le groupe GDM (0,01 ± 0,10 vs. 0,04 ± 0,09 mmol/l ; P < 0,001). Les valeurs de cétonémie mesurées avant le repas de midi et avant le repas du soir étaient plus basses dans le groupe témoin que dans le groupe GDM (P = 0,002 et P = 0,005) ; les valeurs de cétonémie à jeun ne différaient pas entre les deux groupes. 47 % des femmes avec GDM contre seulement 12 % des femmes du groupe témoin ont présenté au moins un épisode cétonémique ; dans le groupe GDM les glycémies les plus basses de fin d’après-midi étaient en corrélation avec les cétonémies les plus élevées ; les femmes atteintes de GDM avaient une prise alimentaire et une consommation de glucides plus faibles que celles des témoins (P < 0,001).

Conclusion: Les valeurs de cétonémie au cours de la grossesse d’un groupe de femmes sans trouble de la glycoregulation ont été établies. Les femmes atteintes de GDM ont fréquemment des cétonémies plus élevées que le groupe témoin, surtout en fin de matinée et fin d’après-midi. Si des valeurs de cétonémie élevées peuvent être mises en rapport avec des comportements alimentaires restrictifs, le suivi de la cétonémie au cours de la grossesse pourrait être utile.

Mots-clés : Diabète gestationnel · Cétonémie · Cétonurie.
Today's ever-increasing prevalence of gestational diabetes (GDM) can be explained by the fact that women are tending to become pregnant later in life [1] (a risk factor for insulin resistance) [2] and by the rising prevalence of excess weight in the general population [3]. The occurrence of diabetes during pregnancy is a major public health issue: it has been shown that the mother's glycaemic level correlates perfectly with a range of critical parameters, such as the child's birth weight, death in utero, perinatal mortality, hypoglycaemia, etc. [4]. Despite a lack of consensus, the mere suggestion of a potential public health problem has prompted industrialized countries to propose systematic screening and diagnosis. Therapeutic management is relatively simple and aims at obtaining correct glycaemia levels through prescription of a carbohydrate- and energy-controlled diet. If the latter is not successful in controlling blood glucose, insulin therapy is recommended (international recommendations) [5].

One potential consequence of an over-restrictive caloric diet is an increase in blood ketone levels. A number of studies have raised questions concerning the role of blood ketone body levels during pregnancy [6,7]. The potential relationship between ketonemia and fetal malformation during the first trimester of pregnancy has been explored in terms of embryos in culture [8]. Other work has reported a relationship between blood ketone body levels during the 2nd and 3rd trimesters and brain maturation [7]. Two studies have reported a correlation between acetonuria during pregnancy and lower intellectual quotients in children born to diabetic mothers [9,10]. This correlation was not confirmed by Rizzo et al., although the authors did reveal a negative correlation between maternal β-hydroxybutyrate concentration and the child's mental development at the age of 2 despite the fact that maternal diabetes had been well managed during pregnancy and that ketonuria was infrequent [10]. Most maternal metabolic substrates cross the placental barrier and are thus received by the fetus in a dose-dependent manner [11]. Maternal fuels can affect fetal development both qualitatively and quantitatively. Changes in fuel concentrations can not only influence organogenesis in early pregnancy but can also lead to more subtle variations in maturation during the third trimester. The studies performed to date have determined fasting plasma β-hydroxybutyrate levels: significantly higher levels have been reported in women with postgestational or gestational diabetes compared to healthy controls [7]. We now possess a micromethod dry strip technique for determining capillary blood ketone body levels. Indeed, self-monitoring of finger capillary blood levels during pregnancy is already indispensable for knowing whether or not glycaemic targets have been met. Furthermore, one of the latest meters for finger capillary blood glucose measurement can also be used to determine ketonemia [12,13]. We previously reported preliminary results on blood ketone levels in pregnant women but in absence of data on food and carbohydrate intakes [14].

The goal of the work was to measure ketonemia in a control population of non-diabetic, pregnant women and a population of women suffering from GDM. We first sought to define an usual ketonemia threshold for the control population. We then compared this value to the GDM population and attempted to correlate the result with dietary behavior.

**Materials and methods**

Subjects: pregnant women presenting in our obstetrics departments were systematically screened for GDM between the 24th and 28th weeks of pregnancy (post-amenorrhea). Screening was performed using a 75 g OGTT (WHO guidelines). A diagnosis of GDM was made when glycaemia 2 hours after ingesting 75 g of glucose was ≥140 mg/dl [15]. When the glycaemia value was <140 mg/dl, the patient was classified as a control subject.

Therapeutic management: each subject was monitored in accordance with the appropriate guidelines; in addition, the control subjects agreed to perform glycaemia and ketonemia self-monitoring 3 times a day, i.e. upon waking, before the midday meal and before the evening meal. The two parameters were measured one after the other using two separate drops of blood from the same finger. In addition, women with GDM were asked to measure their postprandial glycaemia (but not postprandial ketonemia). All subjects measured their fasting ketonemia in the morning upon waking. The different parameters were recorded from the diagnosis until the end of the study (37 weeks of amenorrhea). We decided to stop the study at this time point in both groups, in order to be certain that we were performing a truly comparative, inter-group analysis over the same period (early delivery is often induced in women with GDM). Patients with GDM were treated with a personalized diet, with minimum thresholds of 25 Kcalories per Kg body weight per day and a 42% carbohydrate content. After 10 days on the diet, insulin therapy was initiated if the fasting glycaemia value was ≥95 mg/dl and/or if postprandial glycaemia was ≥120 mg/dl.

The control subjects did not receive any particular instructions concerning nutrition. In both groups, subjects kept a 24-hour food record twice a week (for a different day each week) until the end of the study.

Measurement methods: glycaemia during the OGTT was measured using the glucose oxidase method. Ketonuria measurement was performed using Ketodiabur® urine strips (colorimetric reaction between nitroprusside and ketone bodies: acetooacetate and acetone). The level of urinary acetooacetate was initially scored on the strip's four-point scale, ranging from 0 (minimum) to +3 (maximum). In fact, most positive ketonuric samples scored +1: hence,
subsequent statistical analyses involving ketonuria were based simply on its presence or absence. Glycaemia measurement was performed using a OptiumTM meter and Optium™ Plus capillary blood test electrodes (Abbott, Division Abbott Diabetes Care, Rungis, France). Measurement of capillary blood ketonemia was carried out using the Optium™ meter and Optium™ β-Ketone test strips. β-hydroxybutyrate (βOHB) is measured in the MediSense Optium β-Ketone electrode. The Optium™’s onboard memory enabled a posteriori validation of the values entered by the subjects in their monitoring diaries. The reproducibility of the method used is excellent and is comparable to the laboratory-based reference method, even though the reader has a tendency to slightly overestimate blood βOHB concentrations [13]. Repeat analysis resulted in CVs of 3.3% [16]. Precision was assessed using intra-assay coefficients of variation for 90 replications and resulted in CVs of 8.2% [17]. The correlation between ketone test strips results and ketone lab’s results were excellent (r=0.959) and demonstrated a strip sensitivity between 0.1 and 2 mmol/l [18].

Clinical data: the following parameters were noted for each subject: pre-pregnancy body mass index (BMI), BMI at the time of GDM diagnosis (i.e. inclusion), BMI at the end of the study and weight gain over the study period.

Statistical analysis: the results were analyzed from the moment of the diagnostic OGTT up to the 37th week of pregnancy, and are expressed here as means ± standard deviation (SD). Self-monitoring data were analyzed with SAS software version 8.2 (SAS Institute, Cary NC, USA). The two groups’ initial compatibility was tested using Student’s test for quantitative or continuous variables. A mixed linear model for repeated measures was used to compare the groups in terms of changes over time in glycaemia and ketonemia: it treated the group, and the day and time of the reading as fixed effects and the subject as a random effect. Cross-correlations between pairs of variables were identified using linear regression or cross-tabulation, as appropriate. Determination of the normal ketonemia threshold was performed using descriptive statistics and via examination of the threshold value’s predictive characteristics in terms of sensitivity, specificity and Youden index.

The study protocol was approved by the local Investigational Review Board and all subjects had given their informed, written consent.

Results

Study population characteristics

Fifty-six women presenting a normal OGTT (control group) (2-hour post-load glycaemia value: 103±19 mg/dl) and 49 women presenting GDM (2-hour post-load glycaemia value was 188±128 mg/dl) were included; age, BMI, and weight gain are shown in table I. The two groups did not differ in terms of age; the pre-pregnancy BMI and BMI on inclusion were higher in the GDM group than in the control group (P<0.007). The weight gain differed significantly (P<0.01): women with GDM gained less weight than those in the control group. The results of the screening test differed between the two groups because it represented the principal inclusion criteria (P<0.001) (table I).

Analysis of ketonemia

Only values stored in the meter’s memory were taken into consideration: the results are summarized in table II. Mean ketonemia was lower in the control group than in the GDM group (0.01±0.10 vs. 0.04±0.009 mmol/l; P<0.001).

Table I

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group N=56</th>
<th>GDM group N=49</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.98±4.86</td>
<td>31.35±5.39</td>
<td>P=0.18</td>
</tr>
<tr>
<td>WHO glycaemia test (mg/dl)</td>
<td>103±19</td>
<td>188±128</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Pre-pregnancy BMI (kg/m²)</td>
<td>23.14±4.62</td>
<td>25.96±5.81</td>
<td>P=0.007</td>
</tr>
<tr>
<td>BMI on inclusion (kg/m²)</td>
<td>26.36±4.80</td>
<td>29.20±6.27</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>14.49±4.93</td>
<td>9.25±5.52</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Table II

| Ketonemia values for the control and gestational diabetes (GDM) groups (mmol/l). |
|-----------------------------------------------|---------------------|----------------|
| Control group N=56                          | GDM group N=49      | P-value       |
| Mean±SD                                      | Mean±SD             |               |
| Mean ketonemia                               | 0.01±0.1            | 0.04±0.009    | P<0.001 |
| Fasting ketonemia on waking                  | 0.01±0.11           | 0.01±0.06     | P=0.17  |
| Ketonemia before midday meal                 | 0.01±0.08           | 0.01±0.06     | P=0.002 |
| Ketonemia before evening meal                | 0.02±0.09           | 0.05±0.1      | P=0.005 |
Analysis of the "time of day" effect showed a diabetes-time relationship between the two groups (P<0.001): this meant that the fluctuations in ketonemia over time differed between the two groups, and thus prompted us to analyze the data for each portion of the day. Fasting ketonemia did not differ between the two groups; ketonemia values measured before the midday meal were lower for the control subjects than for the GDM patients (P=0.002); ketonemia values obtained prior to the evening meal were also lower for the control subjects than for GDM patients (P=0.005).

In addition to the absolute values, we determined the frequencies with which ketonemia exceeded thresholds of 0.1, 0.2, 0.3, 0.4 and 0.5 mmol/l, respectively. There did not appear to be any significant differences in the morning, whereas there were more values over 0.2, 0.3, 0.4 and 0.5 mmol/l for midday and evening readings in the GDM group (P=0.02).

Analysis of glycaemic profiles

The glycaemia data was analyzed in the same way as the ketonemia results, that is to say for each period of the day: upon waking, before the midday meal and before the evening meal. The mean glycaemia was lower in GDM subjects than in controls subjects (83.8±14.7 mg/dl vs. 90.3±18 mg/dl; P<0.01). There were no differences between the two groups in terms of fasting glycaemia upon waking. In contrast, the midday and evening preprandial glycaemia values were both lower in women with GDM than in control subjects (P<0.001) (89.1±19.4 mg/dl vs. 80.1±15025 mg/dl); post prandial glycaemia value was 109.46±21.31 mg/dl in the DG group.

Definition of pertinent ketonemia values for distinguishing between the two groups

To date, "standard" ketonemia has not been defined as such. We sought to define the morning, midday and evening ketonemia values which would best differentiate between the control and GDM groups. For each period of the day, the selected cut-off corresponded to a value offering the best compromise between sensitivity and specificity and thus obtain optimal discrimination between GDM subjects and control subjects.

For the morning measurement, a 0.1 mmol/l threshold gave a sensitivity of 66.7% and a specificity of 70.6%: for patients with GDM, 66.7% of the individuals reached or exceeded the 0.1 mmol/l threshold at least once, whereas 70.6% of the control subjects never reached or exceed this value.

With respect to midday ketonemia, a threshold of 0.2 mmol/l was selected, with a sensitivity of 64.3% and a specificity of 84.3%; this yielded positive and negative predictive values of 77.1% and 74.1%, respectively. Very similar results were obtained for evening ketonemia.

Table III

<table>
<thead>
<tr>
<th>Nutritional behavior in the two groups.</th>
<th>Control group</th>
<th>GDM group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=56</td>
<td>N=49</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>P-value</td>
</tr>
<tr>
<td>Kilocalories</td>
<td>2326±547</td>
<td>1901±379</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>90±25</td>
<td>94±23</td>
</tr>
<tr>
<td>Lipids (g)</td>
<td>98±34</td>
<td>77±27</td>
</tr>
<tr>
<td>Carbohydrates (g)</td>
<td>271±22</td>
<td>208±45</td>
</tr>
</tbody>
</table>

Identification of a relationship between ketonemia and pre-pregnancy BMI

The women were classified into 3 groups according to their pre-pregnancy BMI (lower than 23 kg/m², between 23 kg/m² and 27 kg/m² and greater than 27 kg/m²). The groups differed in terms of the number of high ketonemia values recorded: when the pre-pregnancy BMI was greater than 27, the highest ketonemia values were recorded by subjects in the GDM group (P=0.04).

Nutritional monitoring and therapeutic management

The women with GDM reported lower intake than the controls (1901±379 Kcalories vs. 2326±547 Kcalories) (P<0.001). This presumably corresponded to the reporting carbohydrates and lipids, whereas the quantity of proteins was the same in both groups (table III). We did not detect any correlation between food intake parameters and ketonemia. In the GDM group, there appeared to be a relationship between the highest ketonemia levels and the lowest glycaemia values before the midday meal and before the evening meal. Further analysis showed that this relationship approached significance only in patients not treated with insulin (n=30) and solely for late morning glycaemia measurements (P=0.051).

Relationship between morning ketonuria and the previous evening’s ketonemia

For control subjects, we observed a correlation between morning ketonuria (in terms of its presence or absence) and the previous evening’s ketonemia value (P=0.006). This correlation was not detected for women with GDM.

Analysis of the chronicity of ketonemic excursions in patients with gestational diabetes

In order to give clinical value to the existence of high ketonemia levels, we analyzed the phenomenon’s chronicity. A chronic increase in ketonemia levels was defined as the unbroken period during which each day is a part of a
sliding 7-day interval containing more than 25% of late morning or evening ketonemia values over the corresponding thresholds. According to this definition, 6 (12%) of the control subjects experienced at least 1 chronic increase in ketonemia levels (with a total of 9 episodes) vs. 23 (47%) in the GDM group (with a total of 37 episodes). Of these 23 women, 11 (48%) had experienced at least 2 chronic increases in ketonemia levels. In the control group, the episodes lasted with an average episode length of 7 days; for women with GDM, the average episode duration was 13.8 days.

**Discussion**

The nutritional management of GDM has been based on guidelines from diabetology societies, with therapeutic practice being modulated according to glycemic targets: a full consensus has not yet been defined [19,20]. Ketonuria is often monitored but clear management guidelines have not yet been established. Home-based methods of measuring ketonemia are now available and we believe that it is important to evaluate the utility of this tool in routine clinical practice (particularly in cases of GDM) and to define threshold values in a GDM-free population.

We are not aware of studies having quantified ketonemia during routine management of GDM or having monitored ketonic profiles in pregnant control subjects. We chose to target the start of our study at the 24th week of amenorrhea (since this time point corresponds to the GDM screening test in France) and to situate the study end date at the 37th week (in order to avoid different follow-up periods in each two groups – in women with GDM, delivery is often induced before full term after the 37th week of amenorrhea). The two groups of women observed here had the same mean age and age range. A high BMI (both pre-pregnancy and on inclusion) corresponds to the very cause of GDM; the lower weight gain in GDM patients probably corresponds to the fact that the women themselves adopt a more restrictive carbohydrate- and caloric nutritional program than that prescribed when they become pregnant or once GDM is diagnosed. This weight effect may well be associated with a certain degree of calorie restriction and could potentially trigger the appearance of ketonemia.

Ketonemia is a parameter which is likely to be significantly higher in a pregnant woman with GDM that in a healthy counterpart, although the latter individuals typically show a greater dispersion of ketonemia values (a phenomenon that we are unable to explain by analysis of the present study population). Although fasting ketonemia does not really appear to differ, midday and evening ketonemia values are higher in GDM and appear to have more discriminating power. If ketonemia were to be considered as a pathological criterion, the pre-midday meal and pre-evening meal values should be measured rather that the traditionally measured fasting value. It appears that more than half the women with GDM displayed high ketonemia values, with these excursions lasting for several days or weeks.

This study did not enable us to attribute any particular significance or prognostic value to the observed values. It is noteworthy that the values in GDM patients clearly differed from those observed in a control population: this observation should prompt further thought. In the absence of a defect in insulin secretion, ketonemia reflects catabolism. Pregnancy is characterized by increased catabolism, notably during the 3rd trimester; this hypercatabolism may well be related to a more pronounced insulin-resistant state seen during the 5th trimester of pregnancy (and which, on a day-to-day basis, becomes more intense in the late afternoon), as well as to lower hepatic glucogen reserves during pregnancy. Our analysis of the subjects’ food records showed that GDM patients consumed less calories and had a lower carbohydrate intake than prescribed, when compared with control subjects. In view of the study methodology used, there was no statistical relationship between carbohydrate intake and ketonemia. The food records were only filled out twice a week, and the days recorded did not necessarily correspond to the days with the highest ketonemia values. We detected a correlation between the lowest evening glycaemia values and the highest ketonemia measured at the same time of day. This result rules out an insulin deficiency, and so it is probable that carbohydrate restriction practiced by the women themselves is one of the explanatory factors. Since this behavior does not correspond to the prescribed nutritional guidance, it is possible that knowledge of their glycaemia levels and fear of insulin therapy drove these women to adopt the restrictive behavior observed here, despite the nutritional advice given to the study participants at the time of GDM diagnosis as part of their therapeutic care. Furthermore, the induced food habits resulted in the women having food intakes below the general guidelines for pregnancy; this could perhaps explain the elevation in blood ketone levels.

Literature reports have focused exclusively on ketonuria. Indeed, a negative correlation between ketonuria and intellectual quotient in children born to diabetic mothers has been reported [9,21]. A relationship between the existence of high ketonemia during the last trimester of pregnancy and delayed educational development has also been suggested [7]. These studies merely determined fasting βOHb levels in the morning. Women with GDM had significantly higher values than control subjects (0.17±0.08 mmol/l vs. 0.14±0.05 mmol/l; P<0.002), whereas the present study did not reveal any inter-group differences for morning ketonemia. Differences were observed for midday and evening values. This disparity could also be explained by the measurement method. Ketone bodies and βOHb can be measured by a variety of methods. All these
techniques have to deal with the volatile nature of ketone bodies. Unfortunately, neither of the above-cited studies mentions these aspects or describes the measurement conditions. This situation can generate variability and discrepancies and may well explain the disparity between our results and those reported. The dry chemistry technique used here guarantees a high degree of reproducibility and quality, given that there is little time for the ketones’ volatility to influence the result.

Montelongo et al. reported a βOHB level between 3 and 5 times greater that the value usually found in women with GDM and pregestational type 1 diabetes for each trimester [21]. The low number of subjects made it difficult to draw firm conclusions. Jovanovic et al. confirmed that βOHB levels were negatively correlated with fasting glycaemia after 6 weeks of pregnancy in non-diabetic women. This study did not reveal an association between ketone bodies and congenital malformation or death in utero [7]. This aspect has been mentioned for in vitro animal models [22,23]. However, the values reported in these studies are 1.6 to 3 times higher than those measured here; indeed, the levels observed in the present study are far below those generally considered to be “at-risk”. However, we are not talking about the same issues: the usually cited values correspond to a risk of malformation which only exists during the 1st trimester; our study took place during the care that guarantees a high degree of reproducibility and quality, and those reported. The dry chemistry technique used here may well explain the disparity between our results and those reported.

This aspect has been mentioned for in vitro animal models [22,23]. However, the values reported in these studies are 1.6 to 3 times higher than those measured here; indeed, the levels observed in the present study are far below those generally considered to be “at-risk”. However, we are not talking about the same issues: the usually cited values correspond to a risk of malformation which only exists during the 1st trimester; our study took place during the care period for GDM, i.e. the 3rd trimester. At this latter stage, the malformation issue is absent and the only remaining questions are nutritional ones. Our results appear to demonstrate that different types of nutritional behaviour in women with GDM lead to different blood ketone levels, although the latter do not reach values likely to correspond to a risk of ketone decompensation.

We believe that the present results are noteworthy: if ketonemia indicates overly restrictive behavior, it is clear that this parameter could be usefully employed for monitoring adherence to the nutritional recommendations prescribed to women with GDM. This work has enabled the establishment of ketonemia reference standards in non-diabetic, pregnant women. For women with GDM, we are not in a position to conclude whether or not their ketonemia levels have clinical significance in terms of the pregnancy outcome or the health of the child. Ketonemia values differ from those recorded in control subjects and this difference is surely not irrelevant. Before drawing conclusions, a study needs to be performed in order to be certain that higher ketonemia during pregnancy has a detrimental prognostic significance for subsequent fetal development. This parameter could be also useful to detect the adherence to the nutritional advices.

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References