Introduction

The increasing prevalence of diabetes in the general population and getting pregnant in older ages has caused an increased number of diabetic pregnancies.\textsuperscript{1,3} Gestational diabetes mellitus (GDM) affects 3%-6% of all pregnancies.\textsuperscript{4,6} There is an increased risk of maternal and fetal complications associated with both overt and gestational diabetes.\textsuperscript{7,8} With overt diabetes, the risk of stillbirth and neonatal death will be increased 5 and 3 times respectively.\textsuperscript{3,10} In women with elevated fasting glucose levels in GDM, the rate of intrauterine fetal death (IUFD) is elevated.\textsuperscript{11} Perinatal complications may be reduced in women who maintain their euglycemia during pregnancy.\textsuperscript{12} The risk of late pregnancy fetal death in pregnancies complicated with diabetes promoted recommendations for fetal surveillance programs.\textsuperscript{13} American College of Obstetrics and Gynecology (ACOG) recommends initiating tests between 32 and 34 weeks of gestational age. None of these tests has been evaluated in a randomized clinical trial. The purpose of the present systematic review is to assess the effects of fetal testing on reducing fetal mortality in pregnancies with diabetes, through reviewing the observational studies. The research question was whether there is sufficient evidence in the studies to support antenatal fetal assessment in diabetic women with good blood sugar control. No randomized clinical trial has been conducted to investigate this claim.

Methods

A systematic review of the literature was performed to identify cohort and observational studies evaluating the effects of fetal testing on reducing fetal mortality in pregnancies with diabetes. The databases were searched to find English and Persian articles published from 1975-2018 about antenatal fetal assessment in pregnancies complicated with diabetes. Relevant sources cited in the selected publications were also searched manually. Keywords were GDM, pregnancy, fetal testing, fetal surveillance, NST, BPP, and CTG. A total of 1954 studies were identified. Of these, 1913 were excluded on the basis of title and abstract review. Among the 41 studies retrieved for detailed full-text analysis, a total of 10 fulfilled the inclusion criteria for the analysis. Still birth rate and cesarean rate were 5.6/1000 and 418/1000, respectively. In diabetic pregnant women (gestational and overt diabetes) with well controlled blood sugar who did fetal surveillance tests, the intrauterine fetal death (IUFD) rate was not different with general population.

Conclusion

As this systematic review suggests, fetal mortality is rare with fetal surveillance tests in pregnant diabetic women with good blood sugar control. No randomized clinical trial has been conducted to investigate this claim.

Abstract

Introduction: Various fetal surveillance tests are proposed to reduce the rate of stillbirth in diabetic mothers; however there is no sufficient evidence to support this. The purpose of the present systematic review was to assess the effects of fetal testing on reducing fetal mortality in pregnancies with diabetes.

Methods: The databases were searched to find English and Persian articles published from 1975-2018 about antenatal fetal assessment in pregnancies complicated with diabetes. Relevant sources cited in the selected publications were also searched manually. Keywords were GDM, pregnancy, fetal testing, fetal surveillance, NST, BPP, and CTG. A total of 1954 studies were identified. Of these, 1913 were excluded on the basis of title and abstract review.

Results: Among the 41 studies retrieved for detailed full-text analysis, a total of 10 fulfilled the inclusion criteria for the analysis. Still birth rate and cesarean rate were 5.6/1000 and 418/1000, respectively. In diabetic pregnant women (gestational and overt diabetes) with well controlled blood sugar who did fetal surveillance tests, the intrauterine fetal death (IUFD) rate was not different with general population.

Conclusion: As this systematic review suggests, fetal mortality is rare with fetal surveillance tests in pregnant diabetic women with good blood sugar control. No randomized clinical trial has been conducted to investigate this claim.

Article info

Article History:
Received: 7 Nov. 2020
Accepted: 30 Jan. 2021
e-Published: 18 Mar. 2021

Keywords:
• Antenatal fetal testing
• Diabetic pregnancies
• Pregnancy outcomes
• Fetal surveillance
• Pregnant women

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Iranian Research Institute for Information Science and Technology were searched to find English and Persian articles published from 1975-2018 about antenatal fetal assessment in pregnancies complicated with diabetes. Relevant sources cited in the selected publications were also searched manually. Unpublished studies and documents (grey literature) and studies presented in conferences were reviewed. The searched keywords were: GDM (gestational diabetes mellitus), pregnancy, fetal testing, fetal surveillance, NST, BPP, and CTG. The tests used to assess fetal health in diabetic mothers included biophysical profile (BPP) ultrasound, non-stress test (NST), and contraction stress test (CST). Unexplained cases of stillbirth were reviewed and the cases with a specific cause such as anomaly, preeclampsia, and placental abruption were excluded from the study.

**Study selection**

Subjects were pregnant women with pre-gestational or GDM who followed a particular regimen or took insulin (or other blood sugar reducing medications) to control diabetes and were under prenatal surveillance for blood sugar control. Inclusion criteria for papers were defined as references to the method of fetal assessment (NST, CST, BPP), class of diabetes, gestational age in the initial testing, test frequency, pregnancy, neonatal outcomes and precise control of blood glucose. When both biochemical and NST or biophysical tests had been performed, NST and BPP were reviewed. Exclusion criteria were: articles with faulty statistics, letters to editor or suggestions; articles in languages other than Persian and English; articles with poor quality; and fetal surveillance methods that are no longer used such as urine estradiol.

**Data extraction and quality assessment**

Extracted articles using the above-mentioned keywords were selected by 2 specialists at three stages. First, all of the titles were reviewed then the articles which did not meet the research goals were excluded. Abstracts and full texts of the articles were then reviewed and those articles that met the exclusion criteria or had little relevance to the research goals also were excluded. The selected studies were examined by two specialists in terms of risk of bias. Cases of disagreement between the two assessors were referred to the third specialist. The necessary extracted pieces of information were summarized in the extraction form. The information included the first author’s name, publication year, country of origin, type of study, sample size, type of tests, and initiation time of tests. The outcome variables included incidence of IUFD (after 25 weeks of gestational), incidence of non-anomalous neonatal death, the incidence of delivery due to abnormal fetal assessment tests, number of performed tests for each patient, gestational age of fetal mortality, and White’s class of the highest mortality rate.

Endnote X5 software was used for organizing, reviewing the titles and abstracts as well as identifying the duplicates. Ten studies met the inclusion criteria. Daily blood sugar control was reported in all of the studies. Add back tests were described in 9 studies. No randomized controlled study was found. Meta-analysis and comparative analysis were conducted on the findings when possible. Other findings were reported descriptively. Fetal testing had begun from 28 to 36 weeks’ gestational age.

**Statistical methods**

Heterogeneity across the study was investigated using the Cochrane Q-test and the I² Index. If I² was less than 50% we used fix effect model with the Cochrane Mantel-Haenszel approach, if it was more than 50% or P value less than 0.05 we used random-effects model to evaluate the comprehensive effect. Because outcomes quantify values were small so log transformation was used. Statistical analysis was done with CMA v. 2.0 software. P value less than 0.05 considered as statistically significant.

**Results**

**Search results and study characteristics**

A total of 1954 articles were found; 1944 articles were excluded by title abstract and inadequate data and irrelevancy (Figure 1). One of the selected articles was excluded due to no access to its full text. In the end, ten articles were selected for meta-analysis, including 3140 participants. Nine studies were prospective observational and one was a case-control study. In 6 articles the IUFD or neonatal death was the primary outcome. Characteristics of the selected articles are summarized in Table 1. Patients with diabetes of class A1 or A2 were 2213 patients, and 927 patients were in class B to F.

**Meta-analysis results**

IUFDs without known reasons were reported in 9 cases which was 5.6/1000 patients. Two cases were in...
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Diabetic class A2, 4 cases in class B and, 3 cases in class C. Gestational age of pregnancies with IUFDs were 5 cases in term pregnancies (37-38 weeks of gestation) and 4 cases in preterm pregnancies (33-36 weeks of gestation). Heterogeneity of the studies was not significant (Q-value=7.51, P-value=0.58, I²=0.00). The meta-analysis results showed that IUFD event rate in patients who underwent prenatal tests was 5.6/1000 (Logit P= -5.17, 95% CI: -5.73 to -4.62, P< 0.001) which is statistically significant. Forest Plot for the composition of the studies is presented in Figure 2.

The rate of neonatal death (without anomaly) was reported in 8 studies; 3 cases were reported in 2 studies with 2 preterm births, but they were not iatrogenic.

The time interval between the last test and delivery was reported in 6 studies. Two cases of fetal death happened for less than four days from the last test. Seven of 9 IUFD cases took place in term pregnancies.

The rate of cesarean section was reported in 6 articles being 41.8% which had not been compared with a nondiabetic population. Heterogeneity of the studies was significant (P value<0.001, Q-value=110.86, I²=95.49). The meta-analysis results showed that the cesarean prevalence in mothers who had used prenatal tests was 56/1000 (Logit P = -0.87, 95% CI: -1.63 to -0.11, P value=0.025) which is statistically significant. Forest Plot for the composition of the studies is shown in Figure 3.

The number of tests performed was reported in 6 studies. Of the 15172 preliminary tests, 10.6% (n=1608) were abnormal, of which 292 (11.0%) cases had ended in delivery which indicates a high rate of false-positive results.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>First test</th>
<th>Frequency of test</th>
<th>Total fist tests</th>
<th>Second test</th>
<th>GA</th>
<th>IUFD</th>
<th>Neonatal death</th>
<th>Cesarean (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kjos et al</td>
<td>1501</td>
<td>NST &amp; AF</td>
<td>2/week</td>
<td>8936</td>
<td>BPP</td>
<td>32-34</td>
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<td>Lagrew et al</td>
<td>614</td>
<td>NST</td>
<td>NR</td>
<td>NR</td>
<td>CST-BPP</td>
<td>27</td>
<td>3</td>
<td>1</td>
<td>NR</td>
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<tr>
<td>Olofsson et al</td>
<td>61</td>
<td>NST</td>
<td>1-2/week</td>
<td>1882</td>
<td>OCT</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>39.2</td>
</tr>
<tr>
<td>Golde et al</td>
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<td>2/week</td>
<td>672</td>
<td>BPP</td>
<td>34</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Dicker et al</td>
<td>98</td>
<td>BPP</td>
<td>weekly</td>
<td>978</td>
<td>BPP-CST</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>34.7</td>
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<tr>
<td>Gabbe et al</td>
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<td>CST-NST</td>
<td>weekly</td>
<td>NR</td>
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<td>34</td>
<td>3</td>
<td>2</td>
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<td>2/week</td>
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<td>NST-CST</td>
<td>35-36</td>
<td>0</td>
<td>0</td>
<td>NR</td>
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<tr>
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<td>NST</td>
<td>2/week</td>
<td>1976</td>
<td>BPP</td>
<td>28-32</td>
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<tr>
<td>Johnson et al</td>
<td>238</td>
<td>BPP</td>
<td>1-2/week</td>
<td>1024</td>
<td>BPP</td>
<td>30-32</td>
<td>0</td>
<td>0</td>
<td>23.0</td>
</tr>
<tr>
<td>Devoe et al (case-control)</td>
<td>18-18</td>
<td>BPP</td>
<td>Every other week</td>
<td>NR</td>
<td>NR</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>NR</td>
</tr>
</tbody>
</table>

GA: gestational age in the beginning of the test; NST: non stress test, AF: amniotic fluid; NR: not reported; BPP, Biophysical profile.

Table 1. Characteristics of the selected articles in the systematic review

GA: gestational age in the beginning of the test; NST: non stress test, AF: amniotic fluid; NR: not reported; BPP, Biophysical profile.

APGAR score less than 7 in first or fifth minutes was reported in 6 articles. It was reported in 1.6% to 14.2% of patients, the mean percentile was 4.6%.

The frequencies of patients with abnormal primary tests were reported in 8 articles. It was reported in 3.3 to 23.5% of patients which needed to a second test, the mean percentage of patients with the abnormal first test were 12.8% of patients.

Delivery due to abnormal fetal surveillance tests were reported in 6 studies. It was reported in 0.9 to 11.6% of patients, the mean percentage was 6.4% of patients.

Preterm deliveries due to abnormal test results were reported in 6 studies with a 25/1000 event rate. There is a concern about the fact that these tests might increase preterm pregnancy; given the high rate of false-positive results.

The number of tests performed was reported in 6 studies. Of the 15172 preliminary tests, 10.6% (n=1608) were abnormal, of which 292 (11.0%) cases had ended in delivery which indicates a high rate of false-positive results for these tests. Of the whole deliveries due to abnormal test

Figure 2. Forest Plot for the composition of the studies in Still Birth

Figure 3. Forest Plot for the composition of the studies in Cesarean

results, 2.5% were preterm. The number of preliminary abnormal test results was high. The average number of tests for each patient was reported in 6 studies ranging from 5.9 to 30.8 for each patient indicating difference in time of beginning and frequency of the tests.

The gestational age at the beginning of tests was 28 to 34 weeks. The lowest gestational age of IUFD was 33 weeks of gestation in one case of fetal death.

Discussion

The purpose of this systematic review was to summarize the pieces of evidence found in the literature for reducing IUFD in diabetic pregnant women through fetal testing. There were significant differences in clinical and methodological approaches to interventions, outcomes, study design, and rate of bias. Tests had begun from 28 to 36 weeks of gestational age with no relevant explanation. In relation to the outcomes, no comparison of the GDM and pre-pregnancy diabetes was found.

Although the review was concentrated on those interventions that prevented IUFD, this outcome had not been addressed in many of the studies and no randomized clinical trial was conducted to compare the tests with no testing and there were observational studies. Therefore, our comparison was with mortality in the general population.

Unexplained IUFDs were reported in the studies with a 5.6/1000 event rate which is comparable to the IUFD rate in the general population.13,25-27 Perinatal mortality in the nondiabetic pregnancies was reported in 4.5-7.5/1000 between 1988-1995.28 One study on women with insulin-dependent diabetes reported a 1.9% rate of IUFD (25/1000, which was 5 times greater than the general population and reached 1.5% when anomaly cases were excluded) the difference was not significant.29 It seems in diabetic pregnant women (gestational and overt diabetes) with fetal surveillance tests, the IUFD rate is not different from the general population.

IUFD is higher in cases of diabetic nephropathy,29 but fetal deaths in these studies were related to the classes A2 (2 cases), B (4 cases) and C (3 cases). Given the small number of fetal mortalities, a large sample size is needed for a study to reveal the significant changes.

Of the 1407 patients with type 2 diabetes, there were two cases of IUFD with a 1.4/1000 event rate. In other studies, the rate of perinatal mortality in GDM pregnancies was 7/1000.27 The rate of perinatal mortality in diabetic patients did not significantly differ from the general population.30

In other studies, the perinatal death rate was 17.4/1000 in mothers with overt diabetes and it was 5.9/1000 in nondiabetic mothers,31 the rate of perinatal death was lower in present analysis possibly due to exclusion of anomaly-related deaths from the current study.

Two cases of fetal death had happened less than 4 days from the last test. This suggests that the tests cannot guarantee a favorable outcome. Gestational age at the time of IUFD in 7/9 cases was term, possibly suggesting the necessity of running the tests in term pregnancies.

Of the whole deliveries due to abnormal test results, 2.5% were preterm suggesting that fetal complications and abnormal tests are greater in term pregnancies. A large number of tests cost a lot of money and time for both the health system and patients. Further research is required to prove the necessity of performing intensive tests. None of the tests had been assessed using prospective randomized clinical trials and their value relied on their low false-positive rate.

The rate of the Cesarean section had not been compared with the nondiabetic population. Macrosomia related Cesarean section is more common in diabetic patients than in the general population.

The lowest gestational age of IUFD was 33 weeks of gestation in one case of fetal death. The usual time to begin the tests is week 34.31

The present study shows that no study in recent years has addressed the effectiveness of fetal health assessment methods in diabetic mothers. Given the technological advances of medical equipment and fetal assessment methods and control of blood sugar, further research is needed particularly in relation to the type of the most preferable tests.

Most of the studies on fetal health assessment were about pre-pregnancy diabetes which is commonly accompanied by hypertension and it is unknown whether the results would be true in patients with well-controlled uncomplicated diabetes or GDM.

As far as were sought, two systematic reviews were found on this issue. Fuentes and Chez32 reviewed 7 studies and found that the evidence provided for the clinical effectiveness and cost-effectiveness of fetal health testing in well-controlled diabetic patients was inadequate. In another review of 4 articles about GDM, Barak concluded that even by prenatal tests, unexplained third-trimester IUFD is inevitable.27

As this systematic review suggests, fetal mortality is rare with fetal surveillance tests in pregnant diabetic women with good blood sugar control. No randomized clinical trial has been conducted to investigate this claim.

Impact Statement

- It has been known that there is an increased risk of maternal and fetal complications associated with both overt and gestational diabetes. This study revealed that fetal mortality is rare with fetal surveillance tests in pregnant diabetic women with good blood sugar control. No randomized clinical trial has been conducted to investigate this claim and we suggest using this study topic for further researches in future.
Routine antenatal fetal testing in well-controlled diabetic pregnancies

Conflict of Interest
The authors do not have any conflict of interest to declare.

Ethical Approval
This study was registered in Tabriz Aversity of Medical Sciences National Ethical Committee with this registration code (IR. TRZMED.REC.1398.547).

Authors’ Contribution
FR: Study concept, systemic review of literature; SM: Data acquisition, patient selection, study supervision; NN: Data acquisition, patient selection, study supervision; HH: Data gathering, manuscript preparation, statistical analysis; SP: Manuscript preparation, statistical analysis, final edit, supervision over study; MG: Data gathering, manuscript preparation, statistical analysis

Acknowledgements
We would like to thank the deputy of research of the center in which the study was performed.

Funding
None.

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