A health burden risk in newborns from bigeminal pregnancies conceived in vitro

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Abstract

Aim: The aim of our study was to carry out a comparative analysis of the state of development of newborns from bigeminal pregnancies born as a consequence of in vitro fertilization and compare it with twins conceived naturally. Material: 2526 newborns from bigeminal pregnancies born in the years 2003-2009 at the Perinatology and Gynaecology Clinic of the Medical University in Poznan constituted the studied material. Out of this number, 228 twins were conceived as a result of in vitro fertilization (IVP) and 2298 twins were conceived naturally (NP).

Results: This paper provides the characteristics of the state of development of IVF and NP twins on the basis of six somatic features, separately for each sex. The assessment of the overall state of the twins was performed using the Apgar scale. Histopathological examinations concerned the placenta, assessing the degree of morphological-functional disorders. Apart from this, the frequency of incidence of deaths as well as the risk of premature deliveries in both studied groups of twins were also specified. Conclusions: The results obtained by us confirm the thesis that the number and the degree of perinatal complications may be the consequence of multiple pregnancies. The overall state of the twins after in vitro fertilization did not differ from the state of the group of naturally conceived twins. The only confirmed interdependence between in vitro fertilization and perinatal risk occurred in the frequency of newborn deaths.

Key words: in vitro, perinatal complications, bigeminal pregnancy

Introduction

Babies conceived with the help of the in vitro method constitute a significant group of individuals, numbering about 2 million people. It is estimated that in some countries, babies conceived by means of assisted reproduction techniques constitute 3% of births, and according to forecasts, that percentage may increase to 6%. The use of assisted reproduction techniques in medicine is an experiment conducted on man at an unprecedented scale. Like each experiment, it may be successful or not.

Considering the sharp increase in the demand and use of medically-assisted reproduction, it is essential to assess the impact of these techniques on the health of babies conceived using the in vitro method. The medical and developmental effects of in vitro fertilization are still the subject of debates and studies, despite the fact that the MRC Working Party on Children Conceived by in vitro Fertilization, Society for Assisted Reproductive Technology (SART), and The American Fertility Society labelled medically assisted reproduction methods as safe in regards to the offspring’s health [1]. Medical literature provides reports of contradictory results as to the health condition of babies born as a result of in vitro fertilization. Performing long-term studies monitoring the development of these babies is also proving to be rather difficult.

Recently performed meta-analyses of the latest studies on babies born as a result of in vitro fertilization have highlighted a few main medical consequences [2]. The following perinatal problems occur in relation to in vitro fertilization: premature delivery, low birth mass, higher perinatal mortality rate, more frequent congenital diseases [3-5]. At the same time, there are studies with results negating these conclusions, however [6-8]; while their authors admittedly mention the encountered defects, they also conclude that the risk of their occurrence is low and that the results do not indicate the existence...
of drastic differences in the percentage of babies with congenital defects when comparing naturally conceived babies (1.15%) versus IVF conceived babies (1.9%) when considering the parental age, the number of pregnancies and fetuses [7]. In Finland, the health condition of children born after effective in vitro treatment was analysed. Their health condition was compared with a control group composed of babies conceived naturally. In total, 5000 babies were examined. It was observed that the greatest health burden for babies conceived using the in vitro method was the fact that as many as 35.7% of them came from multiple pregnancies, versus only 2.2% in the control group. Therefore, the increased number of perinatal complications could have been the consequence of multiple pregnancies [9].

Treatment with assisted reproduction methods is related with a higher probability of multiple pregnancy. Spontaneous bigeminal pregnancies are observed with a frequency of 1.2% in the general public, and after infertility treatment this fraction increases to 20%. It is commonly known that multiple pregnancies are connected with an increased risk of premature delivery and complications in the newborn period, death in the neonatal period and an increased risk of congenital diseases. Therefore, multiple pregnancies are as such linked with the greatest risk of unfavourable impact on the health and development of neonates. These suggestions are also reiterated in other works [10-12]. They provoke comparison between the developmental state of babies born from multiple pregnancies as a result of the in vitro treatment, and babies coming from multiple pregnancies, but conceived naturally. We hope that the results of our studies on twins will be an important voice in this still ongoing discussion.

The analysis covered the comparison of the developmental state and the overall assessment of the health condition of newborns from bigeminal pregnancies resulting from in vitro fertilization (IVF) and twins conceived naturally (CN). Thus, an attempt was made to find out if in vitro fertilization increases the risk of perinatal complications, or is caused by multiple pregnancy irrespective of the type of conception.

Results

Comparison of developmental state of IVF and NC twins - somatic features compared separately for both sexes

The comparison of somatic features values between naturally conceived twins and twins born after in vitro fertilization found that the studied features have greater values in twins conceived naturally, but the differences were not statistically significant ($p > 0.05$) (Table 1).

On the other hand, the mean values of somatic features in both twin groups, standardised in terms of fetal age, did not differ significantly from each other, but their variances did. Variance for body mass and chest circumference was greater in twins conceived naturally. The great spread of values of these features may result from numerical strength. On the other hand, the spread of the values of head circumference, which is significantly greater in twins after in vitro fertilization, may result from specific cases, possible congenital diseases, e.g. hydrocephalus.

Evaluation of the overall condition of newborns by means of the Apgar scale

In order to study the dependencies of the general state of newborns after IVF from fetal age, chi-square
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Table 1. Comparison of mean somatic features and their variance in the group of twins conceived naturally (CN) and by means of in vitro fertilization (IVF) – data standardized in consideration of the fetal age (*significant at the level of ≤0.05, **significant at the level of ≤0.01)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number CN</th>
<th>Number IVF</th>
<th>Mean CN</th>
<th>Mean IVF</th>
<th>p</th>
<th>Variance CN</th>
<th>Variance IVF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass</td>
<td>2276</td>
<td>218</td>
<td>0.08</td>
<td>0.06</td>
<td>0.73</td>
<td>0.77</td>
<td>0.68</td>
<td>0.02*</td>
</tr>
<tr>
<td>Total body length</td>
<td>2276</td>
<td>218</td>
<td>0.29</td>
<td>0.29</td>
<td>0.95</td>
<td>0.78</td>
<td>0.72</td>
<td>0.12</td>
</tr>
<tr>
<td>Crown-rump length</td>
<td>2272</td>
<td>216</td>
<td>0.24</td>
<td>0.19</td>
<td>0.47</td>
<td>0.88</td>
<td>0.88</td>
<td>0.99</td>
</tr>
<tr>
<td>Head circumference</td>
<td>2276</td>
<td>218</td>
<td>0.40</td>
<td>0.38</td>
<td>0.65</td>
<td>0.60</td>
<td>0.69</td>
<td>0.00**</td>
</tr>
<tr>
<td>Chest circumference</td>
<td>2276</td>
<td>218</td>
<td>0.41</td>
<td>0.39</td>
<td>0.81</td>
<td>1.03</td>
<td>0.91</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

Table 2. Interdependence between the overall condition of twins conceived naturally (CN) or by means of in vitro fertilization (IVF) and the duration of pregnancy (*significant at the level of ≤0.05, **significant at the level of ≤0.01)

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Initial Apgar</th>
<th>Final Apgar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CN</td>
<td>IVF</td>
</tr>
<tr>
<td>Pearson’s chi-square</td>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>Chi-square HC (highest credibility)</td>
<td>0.000**</td>
<td>0.000**</td>
</tr>
<tr>
<td>Spearman R</td>
<td>0.000**</td>
<td>0.000**</td>
</tr>
</tbody>
</table>

Statistics were used. Both variables were dependent variables at the level of $p ≤ 0.01$. Spearman’s correlation, applied to possibly confirm the linear dependence, was positive and also significant at the level of $p ≤ 0.01$ (Table 2).

The mean values of the Apgar scores were calculated (regardless of fetal week) both for twins after IVF and for those conceived naturally. For both groups, the mean value of the initial Apgar score specified in the first minute of life was almost the same, while at the fifth minute, slightly higher in twins conceived naturally. However, values obtained by the t-Student test ($p ≥ 0.05$) described the insignificance of these differences. The spread of the mean Apgar values was greater in twins after IVF in spite of a smaller data set. The variances of both groups differed significantly at the level of $p ≤ 0.05$ for the initial Apgar scores and at the level of $p ≤ 0.01$ for the final Apgar scores (Table 3). This may prove that the overall health condition of newborns after in vitro fertilization is more diversified.

The comparison of pregnancy duration in twins born as a result of IVF versus twins conceived naturally – the risk of premature birth

Investigating the number of births in respect to fetal age in weeks (starting from the 22nd week), an increase in births up until week 37 of pregnancy was observed, both in twins conceived naturally and those conceived using medically assisted reproduction. Furthermore, in both studied twin groups, a decrease in births until week 41 was observed post week 37 (Table 4). This observation is the basis for concluding that pregnancy duration in twins resulting from IVF is the same as in cases of multiple pregnancies conceived naturally, i.e. it does not deviate from the standard. Using Chi² statistics, a correlation was confirmed between the frequency of births of twins after IVF and fetal age at the level of $p ≤ 0.01$ ($p = 0.00677$), with chi-square highest credibility statistics confirming a significant correlation between these two variables ($p = 0.03332$). On the other hand, Spearman R statistics did not display such a linear interdependence between these variables (Table 5).

Placental burdens as strong risk factors

Morphological-functional changes within the placenta may have an impact on intrauterine fetal growth inhibition. These changes concern the placental structure (i.e. the form of the placenta, the type of umbilical cord attachment to the placenta, the umbilical cord length), the limited surface of mother-fetus exchange (infarcts, fibrin mass deposits and calcium salt deposits as well as necrosis), the circulatory disturbances (fetal, maternal and fetal-maternal circulation), inflammatory lesions, and prematurely separation of the placenta. The frequency of occurrence of the above placental burdens in babies conceived naturally and by in vitro fertilisation was confirmed in this study. Therefore, both studied twin types (CN and IVF) were divided into 5 groups
Table 3. Comparison of the mean values in the Apgar scale and their variance in groups of twins conceived naturally (CN) and by way of in vitro (IVF)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>PN</th>
<th>Variance</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CN</td>
<td>IVF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial Apgar</td>
<td>7.49</td>
<td>7.44</td>
<td>0.98</td>
<td>2293 228</td>
</tr>
<tr>
<td>Final Apgar</td>
<td>8.85</td>
<td>8.75</td>
<td>0.42</td>
<td>2292 228</td>
</tr>
</tbody>
</table>

Table 4. Percentage of twins conceived naturally (CN) and by means of in vitro fertilization (IVF) who were delivered in the respective weeks of fetal life (22-41)

<table>
<thead>
<tr>
<th>Week</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>29</th>
<th>30</th>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>0.26</td>
<td>0.26</td>
<td>0.35</td>
<td>0.70</td>
<td>1.92</td>
<td>1.48</td>
<td>1.13</td>
<td>2.09</td>
<td>2.35</td>
<td>3.57</td>
</tr>
<tr>
<td>IVF</td>
<td>0.00</td>
<td>1.77</td>
<td>1.77</td>
<td>0.88</td>
<td>0.88</td>
<td>1.77</td>
<td>2.65</td>
<td>1.77</td>
<td>2.65</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week</th>
<th>32</th>
<th>33</th>
<th>34</th>
<th>35</th>
<th>36</th>
<th>37</th>
<th>38</th>
<th>39</th>
<th>40</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>4.62</td>
<td>5.14</td>
<td>7.93</td>
<td>11.41</td>
<td>16.99</td>
<td>22.39</td>
<td>10.54</td>
<td>4.88</td>
<td>1.39</td>
<td>0.61</td>
</tr>
<tr>
<td>IVF</td>
<td>4.42</td>
<td>2.65</td>
<td>5.31</td>
<td>12.39</td>
<td>14.16</td>
<td>23.89</td>
<td>13.27</td>
<td>7.96</td>
<td>0.88</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Table 5. Interdependence between the fetal age and the frequency of births of twins conceived by means of in vitro fertilization, the results of the chi-square tests and the Spearman correlation test (*significant at the level of ≤0.05, **significant at the level of ≤0.01)

<table>
<thead>
<tr>
<th>Statistics</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson’s chi-square</td>
<td>0.007**</td>
</tr>
<tr>
<td>Chi-square HC (highest credibility)</td>
<td>0.033*</td>
</tr>
<tr>
<td>Spearman R</td>
<td>0.159</td>
</tr>
</tbody>
</table>

Table 6. Incidence (%) of placental lesions in twins conceived naturally (CN) and by means of in vitro fertilization (IVF)

<table>
<thead>
<tr>
<th>Group</th>
<th>Frequency of placental lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>CN</td>
<td>2.44</td>
</tr>
<tr>
<td>IVF</td>
<td>0.0</td>
</tr>
</tbody>
</table>

depending on the number of morphological-functional disorders in their placentas. Group 0 was characterised by healthy placentas, group 1 had placentas with one lesion, group 2 – with two lesions, group 3 – with three lesions and group 4 – with four or more lesions, respectively.

The incidence of the respective types of placental burdens in both twin groups was similar to each other; the only differences concerned the group with three types of morphological-functional disorders occurring in the placenta. This number of placental burdens was found in 13.5% of twins conceived physiologically and in 21.9% of twins after IVF (Table 6).

To compare these frequencies of incidence, a hypothesis was made about the equality of both fractions, i.e. \( \hat{p}_0 = \hat{p}_1 \), \( H_0: 0.1345 = 0.2188 \). It turned out that \( p = 0.0621 \), i.e. \( p > 0.05 \), therefore there was no reason to reject the hypothesis that the fractions are the same in both groups. The conception of a baby by means of in vitro fertilization and morphological-functional changes are independent variables. The values of \( \chi^2 \) statistics greater than 0.05 (\( p = 0.25740 \)) prove this (Table 7). The number of placental burdens, indicating irregularities within the placenta, does not depend on conception resulting from the in vitro method.

Determination of mortality in both groups of twins

The mortalities in twins conceived naturally and by way of in vitro fertilization were compared. In the first group of twins, the frequency of death amounted to 4.6%, in the second group, the frequency was almost twice as high – 8.3% (Table 8).

The hypothesis about the equality of these fractions was rejected, as it appears that the differences between
Table 7. Interdependence between the type of conception of babies conceived in vitro (IVF) and the frequency of incidence of placental loads or mortality rate – the results of the chi-square test and the Spearman’s correlation test (*significant at the level of ≤0.05, **significant at the level of ≤0.01)

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Sum of placental lesions</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$p$</td>
<td>$p$</td>
</tr>
<tr>
<td>Pearson’s chi-square</td>
<td>0.257</td>
<td>0.012*</td>
</tr>
<tr>
<td>Chi-square HC (highest credibility)</td>
<td>0.147</td>
<td>0.021*</td>
</tr>
<tr>
<td>Spearman R</td>
<td>0.96</td>
<td>0.012*</td>
</tr>
</tbody>
</table>

Table 8. Mortality rates (%) in twins conceived naturally (CN) and by means of in vitro fertilization (IVF)

| Death | CN | | IVF | |
|-------|----| |----|---|
|       | Number | % | Number | % |
| No    | 2193  | 95.4 | 209  | 91.7  |
| Yes   | 105   | 4.6  | 19    | 8.3    |

the frequency of deaths in the two studied groups was at the level of $p = 0.0123$. Pearson Chi² statistics proved the existence of a correlation between the conception of a baby by way of in vitro, and the frequency of deaths. Spearman R statistics demonstrated that it was positive and linear (Table 7).

Discussion

The results obtained by us confirm suggestions that the number of perinatal complications may be the result of multiple pregnancy, bearing the greatest risk for negative impacts relating to development. Most of the comparative studies conducted so far have evaluated the development of newborns after IVF in relation to newborns conceived naturally, without differentiating the material in terms of the number of fetuses. Multiple pregnancies as a result of natural conception are much rarer than those after in vitro, yet newborns from multiple pregnancy after IVF are assessed in comparison with naturally conceived newborns coming mostly from single pregnancies. This may explain the reason for observed differences in the frequency of premature deliveries before week 37 of pregnancy [14]. This may also explains the increase in the risk of low birth mass in the IVF group [15, 16].

In our study comparing the condition of newborns from bigeminal pregnancy after in vitro fertilization and the condition of twins conceived naturally, the obtained results confirmed that during the perinatal period, the general condition of twins of both studied groups is similar and does not deviate from the multiple pregnancy standard. Also, examination of placental burdens in both twin groups confirmed the lack of a correlation between the type of conception and the number of disorders in the placenta. The only difference concerning risks associated with in vitro fertilisation occurred in regards to mortality rates in both groups. It was the only confirmed correlation between perinatal risk and the type of conception of a baby. Meta-analysis of 15 independent studies conducted by American scientists also showed that mortality was twice as high in newborns conceived in vitro [17].

However, because no progress has been made in the pharmacological or operational treatment of infertility in recent years, the only effective procedure in a large group of infertile couples is the use of medically assisted reproduction methods. In spite of many difficulties in monitoring the development of babies born after IVF, increasing amounts of published research are allowing for the formulation of views regarding the degree of safety of medically assisted reproduction methods and their impact on the development of babies. It seems that we are now closer to answering the question if treatment with these methods increases the risk of health complications along with their various types.

After gathering larger amount of twins from IVF we plan to analyze the relationship between their developmental status, gender, and zygosity, also in relation to naturally conceived twins. Such analysis may be helpful in more precise assessment of the risk of health complications and potential developmental threats of children conceived by means of IVF. Undoubtedly, the health status of individuals conceived using advanced assisted reproductive technologies constitutes the question of vital importance. Therefore, the relationship revealed in our empiric study can have clinical importance and should constitute a starting point for further research.
Disclosure of interests
The authors have no conflict of interests.

Contribution to authorship
All authors had substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. M. Waszak and K. Cieslik drafted the article and revised it critically for important intellectual content. All authors gave their final approval of the version to be published.

Ethics approval
All the procedures were approved by the Local Ethics Committee of the Medical University in Poznan.

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References

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