(Maternal) death related to in vitro fertilization

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ABSTRACT

Objective: The most severe complication of IVF, death, is reported rarely. IVF-pregnancies are known to have more obstetric complications, which may result in a higher incidence of maternal deaths. In order to demand attention to this severe complication and to prevent recurrence, we collected deaths that may have been related to IVF.

Materials and Methods: All deaths from 1984-2008 were collected by sending a letter to all gynaecologists in the Netherlands, and by retrieving data from a large cohort study examining the late effects of ovarian stimulation (OMEGA), and from the Dutch Maternal Mortality Committee. The total number of women that had had IVF was estimated to be 100,000. Only deaths that occurred within 1 year after IVF were studied.

Results: Six deaths were directly related to IVF (6/100,000). Three women had Ovarian Hyperstimulation Syndrome, two died from sepsis and one was due to a dose error of a local anaesthetic during ovum pick-up. Seventeen deaths were directly related to the IVF-pregnancy (42.5/100,000): pre-eclampsia (n=4), sepsis (n=2), vascular dissection (n=2), pulmonary embolism (n=2), liver failure (n=2), portal hypertension, small vessel disease, meningitis tuberculosa, suicide and amniotic fluid embolism. Eight deaths were not related to the IVF-procedure nor the IVF-pregnancy.

Conclusions: The overall mortality in patients undergoing IVF-procedure was much lower than in the general population, whereas the overall mortality in IVF-pregnancies was much higher compared to the general population. The first observation is probably due to a ‘healthy female effect’ in women undergoing IVF. The high mortality in IVF-pregnancies is probably due to the fact that (donor egg) IVF is succesfully used in women who are older. The fact that only a few mortalities are reported in the literature whereas we calculated six in the Netherlands indicates that there should have been many more cases worldwide. We underline the importance to report all lethal cases and we call on everybody to report lethal cases to the ESHRE Committee ‘Safety and Quality after IVF’.
INTRODUCTION

In vitro fertilization (IVF) is a standard procedure in subfertility treatment. Complication rates seem to be low and are predominantly related to hormonal stimulation and egg collection, e.g. Ovarian Hyperstimulation Syndrome (OHSS), trombo-embolism, abdominal bleeding, adnexal torsion, allergic reaction, apneu and aspiration related to anaesthetics, radicular pain and ureter blockage.\(^1\) In the literature, death related to IVF is reported very rarely. Furthermore, IVF may involve greater obstetric risks, which may cause a higher incidence of maternal death in IVF-pregnancies.\(^2\)

In order to evoke discussion about this severe complication and to prevent recurrence, we initiated a study to collect all (maternal) deaths that may have been related to IVF in the Netherlands.

MATERIAL AND METHODS

We evaluated deaths following IVF in the Netherlands during the period 1984-2008. In 1984, the first IVF-treatment in the Netherlands was performed. No reliable national IVF-complication register exists in the Netherlands yet, but cases have been reported to the national IVF Working Committee. This Committee assesses all reported cases. These cases are re-evaluated and classified in this report. A letter was sent to all gynecologists requesting to report all lethal cases related to IVF-treatment or during a pregnancy after IVF-treatment, that had ever come to their attention.

Cases were also retrieved from a large national cohort study examining the late effects of ovarian stimulation (OMEGA)\(^3;4\) and from the Maternal Mortality Committee (MMC) of the Netherlands Society of Obstetrics and Gynecology. This Committee consists of eight obstetricians and one internal medicine specialist working in the field of maternal medicine. The MMC assesses all maternal mortality cases reported to them voluntarily by gynecologists, obstetricians, midwives and general practitioners. The MMC also performs a cross check of their anonymised cases with vital data from Statistics Netherlands.\(^5\) Maternal death was defined according to the World Health Organization’s (WHO) International Classification of Diseases, tenth revision (ICD-10) as the death of a woman while pregnant or within 42 days of termination of pregnancy, from any cause related to pregnancy (direct
death) or aggravated by pregnancy or its management (indirect death), but not from accidental or incidental causes. Late maternal death was defined as the death of a woman from direct or indirect obstetric causes more than 42 days but less than one year after termination of pregnancy. The maternal mortality ratio (MMR) was defined as the number of direct and indirect maternal deaths per 100,000 live births up to 42 days after termination of pregnancy. Only deaths that occurred within 1 year after IVF were studied. Cases were subdivided into three categories:

A. directly related to IVF-treatment,
B. directly related to IVF-pregnancy,
C. not (known to be) related to IVF-treatment or to IVF-pregnancy.

RESULTS

A. Deaths directly related to IVF-treatment
Six deaths directly related to IVF-treatment occurred in the studied period, with no death reported after 1997. Three women suffered from OHSS of whom two women with Polycystic Ovarium Syndrome died due to Adult Respiratory Distress Syndrome and multi-organ failure, 29 and 35 days after ovum pick-up (OPU), respectively; the other woman died 3 days after OPU because of cerebrovascular thrombosis. All OHSS patients had all their embryos frozen because of the symptoms of OHSS. The first two women had had 10,000 IU of human chorionic gonadotropin (hCG) before OPU, the third patient had received 5,000 IU of hCG. These cases have been described elsewhere. Two other women died due to sepsis, 62 and 31 days after OPU respectively. One other death was due to a dose error of local anesthetic medication just before OPU.

Unfortunately, in the Netherlands we do not have exact figures of the number of women being treated with IVF. We estimate that about 100,000 women have had an IVF-treatment in the period 1984-2008. As we observed six deaths directly related to IVF, the IVF-treatment related mortality was 6.0 per 100,000.

B. Deaths directly related to IVF-pregnancy.
Seventeen deaths during pregnancy were registered in women while pregnant after an IVF-procedure. These occurred in the period 1990-2008. Causes of death were (pre-)eclampsia with cerebral haemorrhage (four cases), sepsis (two cases),
vascular dissection (two cases), pulmonary embolism (two cases), liver failure (two cases, one due to acute fatty liver of pregnancy), portal hypertension (alcohol abuis, only revealed after death, one case), small vessel disease (one case), meningitis tuberculosa (one case), amniotic fluid embolism (one case) and suicide due to postpartum depression (one case). Characteristics are listed in Table I. Eight out of these 17 pregnancies (47%) were twin gestations. Three of these twin pregnancies resulted from gamete donation. One 44-year-old woman had oocyte donation. Her history revealed mild aortic valve insufficiency, chronic obstructive pulmonary disease, and morbid obesity (after gastric banding her body mass index was 38); she died from vascular dissection. One 49-year-old woman went abroad for oocyte donation, since the guideline of the Netherlands Society of Obstetrics and Gynecology advices against IVF with oocyte donation in women over the age of 45.

Table I. Maternal death in IVF-pregnancies

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>IVF/ICSI</th>
<th>Twin pregnancy</th>
<th>Underlying cause of death</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>ICSI</td>
<td>Yes</td>
<td>Obstetric sepsis</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>IVF</td>
<td>Yes</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>IVF</td>
<td>Yes</td>
<td>Eclampsia, cerebral haemorrhage</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>IVF</td>
<td>No</td>
<td>Pre-eclampsia, cerebral haemorrhage</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>IVF</td>
<td>Yes</td>
<td>Acute Fatty Liver of pregnancy</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>IVF</td>
<td>Yes</td>
<td>Small vessel disease</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>IVF</td>
<td>No</td>
<td>Eclampsia, cerebral haemorrhage</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>IVF</td>
<td>No</td>
<td>Aneurysm dissecans</td>
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<tr>
<td>9</td>
<td>50</td>
<td>IVF</td>
<td>Yes</td>
<td>Eclampsia, cerebral haemorrhage</td>
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<td>10</td>
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<td>IVF</td>
<td>Yes</td>
<td>Pulmonary embolism</td>
</tr>
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<td>IVF</td>
<td>No</td>
<td>Amniotic fluid embolism</td>
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<td>12</td>
<td>44</td>
<td>IVF</td>
<td>Yes</td>
<td>Aneurysm dissecans</td>
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<tr>
<td>13</td>
<td>35</td>
<td>IVF</td>
<td>No</td>
<td>Liver failure</td>
</tr>
<tr>
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<td>35</td>
<td>IVF</td>
<td>No</td>
<td>Sepsis</td>
</tr>
<tr>
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<td>38</td>
<td>IVF</td>
<td>No</td>
<td>Portal hypertension, alcohol abuses</td>
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<td>16</td>
<td>31</td>
<td>IVF</td>
<td>No</td>
<td>Meningitis tuberculosa</td>
</tr>
<tr>
<td>17</td>
<td>38</td>
<td>ICSI</td>
<td>No</td>
<td>Postpartum depression suicide</td>
</tr>
</tbody>
</table>
She died shortly after delivery due to eclampsia and cerebral haemorrhage at the age of 50. One 32-year-old woman had IVF with donor sperm. She was admitted at 33 weeks gestation with nausea, vomiting and petechial rash. She had liver-, kidney- and clotting disorders. She died due to acute fatty liver of pregnancy a few days later. Another woman delivered a singleton after donor egg IVF (performed abroad). This 44-year-old Dutch woman died from amniotic fluid embolism. The overall mean age of women, who died due to obstetrical complications in the course of their IVF-pregnancy was 36.4 years (range 28-50 years).

As mentioned before, we do not have exact figures of either the women who underwent an IVF-treatment, nor of those who achieved an IVF-pregnancy. Still, assuming that 100,000 women have had IVF-treatment, and with a pregnancy rate overall during the studied years of 40%, the number of women becoming pregnant after IVF-treatment was 40,000. The maternal mortality ratio was thus 42.5 per 100,000 IVF-pregnancies (17 in 40,000).

C. Deaths not (known to be) related to IVF-treatment or to the IVF-pregnancy.

No relation could be found between the IVF-procedure and subsequent death in eight women, who died within 1 year after their IVF-treatment or during their IVF-pregnancy. Three women were not pregnant after their IVF-treatment: two women committed suicide and one woman died from vascular dissection during hormonal stimulation. The day she died she had an ultrasound examination of the ovaries. Seven follicles were measured and the oestradiol level was 3253 pmol/l. Her medical history was uneventful, but in retrospect her family history showed a brother dying from aneurysm.

In five deaths, the woman was pregnant after IVF-treatment: two women died in a car accident, and three women died due to cancer (one melanoma, one lung and one gastric carcinoma).

DISCUSSION

Deaths directly related to IVF-treatment

In this overview the major causes of death directly related to IVF are OHSS and sepsis. A search in the international literature showed only two case reports of deaths following OHSS after IVF-treatment. Five other fatal IVF-treatments have only been reported in the lay-press. There have been, however, four case reports
about deaths following OHSS, but these four resulted from ovulation-induction and not IVF.\textsuperscript{10,11,12,13}

Since 1997 no more deaths directly related to IVF occurred in the Netherlands. This may be due to better acquaintance with the risks of OHSS and sepsis. The observed lethal cases resulted in recommendations by the national IVF Working Committee, which led to the implementation of less aggressive stimulation protocols and to the cancellation of OHSS-prone cycles.

Venn et al. published the only large cohort study of IVF patients in Australia, including an analysis of overall mortality.\textsuperscript{2} They observed one death that possibly could have been related to IVF-treatment. This was a 23-year-old woman, who died from pulmonary embolism. They concluded that IVF-treatment related mortality was 5.8 (95% CI 0.8-41.5) per 100,000 women treated. We observed an IVF-treatment related mortality of 6.0 per 100,000 IVF-treatments, which is in line with the observations of Venn et al.

Venn et al. compared overall mortality in IVF patients with overall mortality of the general population. They concluded that overall mortality in IVF patients was significantly lower (RR 0.58, 95% CI 0.48-0.69). In the Netherlands, overall mortality of women aged 20 to 50 years in the general population during these years was 71.3 per 100,000 women (2415/3,387,823) resulting in the same conclusion as Venn et al.\textsuperscript{14} The most likely explanation for this difference is the ‘healthy women effect’, i.e. women eligible for IVF-treatment are healthier and have a higher socio-economic status than the general population.

**Deaths directly related to IVF-pregnancy**

Venn et al. reported a maternal mortality ratio of 25.7 maternal deaths per 100,000 IVF-pregnancies. This is significantly higher compared to the general population, which has 10.9 maternal deaths per 100,000 pregnancies.

In our study the maternal mortality ratio in IVF-pregnancies was 42.5 per 100,000. The MMR in the general population in the Netherlands was 12.1 per 100,000 live born children between 1993-2005.\textsuperscript{5} This is in line with the observations of Venn et al.\textsuperscript{2} The higher maternal mortality in IVF-pregnancies can be attributed to an ‘unhealthy female effect’: IVF patients are older and consequently multiple pregnancy and caesarean section rates are higher.

Four women were older than 40 years (41, 44, 44 and 50 years), which is a risk factor for complications in pregnancy.\textsuperscript{15,16} Paulson et al. reported in pregnant
women aged 50 years or older an increased risk of pre-eclampsia and gestational diabetes.\textsuperscript{17} The majority delivered via caesarean section. Källén et al. did not observe a difference in maternal deaths when comparing IVF-pregnancies with spontaneously conceived pregnancies.\textsuperscript{18} However, they only evaluated pregnant women, who delivered a child. They did observe higher obstetric morbidity in IVF-pregnancies, predominantly pre-eclampsia (OR 1.63; 95\% CI 1.53-1.74), placental abruption (OR 2.17; 95\% CI 1.74-2.72) and postpartum haemorrhage (OR 1.4; 95\% CI 1.38-1.5).

In our study, four out of seventeen women with IVF-pregnancies (24\%) became pregnant with donor gametes. Women who became pregnant after IVF with oocyte donation tend to have more obstetrical complications than women who got pregnant after spontaneous conception or after standard IVF-procedure.\textsuperscript{19} Wiggins et al. reported a significantly increased risk of pregnancy-induced hypertension and pre-eclampsia in pregnancies after donor egg IVF compared to pregnancies by standard (autologous) IVF.\textsuperscript{20} This effect could especially be observed in nulliparous women, (37.1\% pregnancy-induced hypertension versus 8\% in the standard IVF group, \textit{p}<0.003). Maternal age was no confounder in this study. Söderström-Anttila et al. also compared donor egg IVF derived pregnancies with those after normal procedure IVF.\textsuperscript{21} They found significantly more bleeding in the first trimester (53\% vs 31\%, \textit{p}<0.01), pregnancy-induced hypertension (31\% vs 14\%, \textit{p}<0.05) and a higher caesarean section rate (57\% vs 37\%, \textit{p}<0.05). In addition to a higher risk of pregnancy-induced hypertension, a higher risk of postpartum haemorrhage has been found.\textsuperscript{22} Krieg et al. found a higher risk of caesarean section, but no higher risk for pre-eclampsia or neonatal complications compared with women of advanced maternal age undergoing IVF with autologous oocytes.\textsuperscript{23} Eight women in our study had a multiple gestation. Twin pregnancies develop more frequently complications such as pre-eclampsia and postpartum haemorrhage.\textsuperscript{15} Wiggins et al. also found more pregnancy-induced hypertension in women being pregnant with a multiple gestation versus singleton after donor egg IVF (OR 4.9; 95\% CI 1.3-18.3).\textsuperscript{20} Although not present in our study, a specific group of patients consists of pregnant women with Turner syndrome. The risk of aorta dissection or rupture during pregnancy in these patients may be 2\% or higher and the risk of death during pregnancy is increased as much as 100-fold.\textsuperscript{24}
Deaths not (known to be) related to IVF-treatment or to the IVF-pregnancy.
The debate about an increased risk of cancer after IVF is ongoing. The only clear-cut association between IVF-treatment and cancer is ovarian cancer, however this appears to be more related to infertility itself rather than to IVF-treatment: OR 2.7 (95% CI 1.49-4.9) before IVF treatment compared with OR 2.08 (95% CI 1.15-3.75) after IVF. In the same Swedish study a non-significant increased risk was noted for malignant melanoma both before (OR 1.21 (95% CI 0.76-1.93) and after IVF (OR 1.32 (95% CI 0.79-2.20). In our study the follow-up (1 year) was too short to make any conclusions about the incidence of cancer after IVF.

Two patients in our study committed suicide. Although there may have been a relation with IVF-treatment, or its negative outcome, one can hypothesize that this could also have happened in case of infertility without IVF, or without infertility in these women.

CONCLUSION

This study illustrates that it remains very difficult to collect data about deaths that could have been related to IVF. It is therefore very difficult to draw firm conclusions from a study on IVF-related death. Data from the literature are sparse as well. The fact that only a few mortality cases have been reported, whereas we calculated six cases of mortality after IVF-treatment within 13 years of practice, suggests that there should have been many more cases worldwide. The data from the Netherlands presented in this study, collected by comparing three databases, are the best estimates we can get.

All cases of maternal mortality in the Netherlands should be reported to the MMC. We identified cases not being reported to the MMC in this study. A reliable classification and assessment of a case of maternal mortality can only be performed by the MMC when sufficient data are available.

The higher risk of complications due to IVF-treatment or IVF-pregnancies underlines the importance of counseling. Women should be counselled preconceptionally about the increased risks during a pregnancy after (donor egg) IVF. They should be educated about signs of danger during pregnancy. They also should be educated about danger signs of OHSS. Obstetricians should also be aware of these risks, and should act accordingly during pregnancy, delivery and puerperium. The IVF-staff
should be reachable 24 hours a day, 7 days per week, for women with complaints foreshadowing OHSS, sepsis and other severe complications.

Assessment of fatal cases by the Dutch IVF Working Committee led to less aggressive stimulation protocols, lower thresholds for cancellation and an increased policy of ‘coasting’ in case of threatening OHSS. The policy of milder stimulation and single embryo transfer should be propagated continuously. This is even more important in women over the age of 40 opting for oocyte donation. In the Netherlands there is an age limit of 45 years for oocyte donation, but also younger women should be counseled about their risks.

In order to increase awareness of serious iatrogenic complications, and especially those with a lethal outcome, and to learn from these cases, it is important that all professionals worldwide report them. National and supranational registries, such as the American Society for Reproductive Medicine (ASRM), the European IVF Monitoring program (EIM) and the World Registry on assisted reproductive technologies (ART) should ask their accredited members to report all cases of maternal mortality, whatever the cause of death. Furthermore, we call on everybody to (anonymously) report lethal cases after IVF-treatment to the ESHRE Committee ‘Safety & Quality after IVF’.
References
