

1 **Maternal death after oocyte donation at high maternal age:**

2 **Case report**

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5 On behalf of the Dutch Maternal Mortality Committee

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59 Abstract

60 Background: The percentage of mothers giving birth over the age of 35 increased in  
61 many western countries. The number of women remaining childless also increased,  
62 mostly due to aging oocytes. The method of oocyte donation offers the possibility for  
63 infertile older women to become pregnant. Gestation after oocyte-donation-IVF,  
64 however, is not without risks for the mother, especially at advanced age.

65 Case presentation: An infertile woman went abroad for oocyte-donation-IVF, since  
66 this treatment is not offered in The Netherlands after the age of 45 years. The first  
67 oocyte donation treatment resulted in a multiple gestation, but was ended by induced  
68 abortion: the woman could not cope with the idea of being pregnant with twins. In the  
69 second pregnancy after oocyte donation, at the age of 50, she was mentally more  
70 stable. The pregnancy, again a multiple gestation, was uneventful until delivery.  
71 Immediately after delivery she had hypertension with nausea and vomiting. A few  
72 hours later she had an eclamptic fit. HELLP-syndrome was diagnosed. She died due  
73 to cerebral haemorrhage.

74 Conclusions: In The Netherlands, the age limit for women receiving donor oocytes is  
75 45 years and commercial oocyte donation is forbidden by law. In other countries  
76 there is no age limit, the reason why some women are going abroad to receive the  
77 treatment of their choice.

78 Advanced age, IVF and twin pregnancy are all risk factors for pre-eclampsia, the  
79 leading cause of maternal death in The Netherlands.

80 Patient autonomy is an important ethical principle, but doctors are also bound to the  
81 principle of 'not doing harm', and do have the right to refuse to give medical treatment  
82 such as IVF-treatment. The discussion whether women over the age of 50 should  
83 have children is still not closed. If the decision is made to offer this treatment to a  
84 woman at advanced age, the doctor should counsel them intensively about the risks  
85 before treatment is started.

86

87 Word count: 312

88 Keywords: maternal mortality, oocyte donation, eclampsia

89 Background

90 In the Netherlands the proportion of women giving birth over the age of 35 increased  
91 from 5.2% in 1980 to 20% in 2003.<sup>1</sup> This has also been reported in other countries.<sup>2</sup>  
92 The number of women remaining childless also increased, mostly due to aging  
93 oocytes.<sup>3</sup> The method of oocyte donation in vitro fertilization (IVF), with oocytes from  
94 younger women, offers the possibility for infertile older women to become pregnant.  
95 Oocyte donation, however, is not without risks for the mother, especially at advanced  
96 age.<sup>4</sup>

97 In The Netherlands, the age limit for women receiving donor oocytes is 45 years.<sup>5</sup> In  
98 many other countries the maximum age is higher and sometimes even without limits.  
99 Also, in The Netherlands, commercial oocyte donation is forbidden by law (so called  
100 embryo law, implemented in 2002). When IVF treatment is declined in a Dutch clinic,  
101 based on national guidelines and laws, some women are going abroad to receive the  
102 treatment of their choice.

103 In this short communication we present a case of maternal death, illustrating that the  
104 application of new technologies of assisted reproduction in high income countries  
105 nowadays creates a new group of women at risk of maternal death.

106

107 Case presentation

108 The woman got pregnant for the first time at the age of 36 years but had a  
109 miscarriage twice. When she was 38 years old, she had two induced abortions. At  
110 the age of 41 and 43 years, she got pregnant after ovulation induction, and gave birth  
111 to a healthy girl and boy respectively. After this, she suffered from secondary  
112 subfertility, but ovulation induction did not result in pregnancy. At the age of 46,  
113 embryotransfer was performed of three oocytes after oocyte donation, in a clinic in  
114 Belgium, resulting in a twin pregnancy. However, she could not live with the idea of  
115 carrying twins. She first opted for termination of pregnancy, but then agreed with  
116 selective foeticide in the same clinic in Belgium. She could still not cope and had an  
117 induced abortion of the second twin in the second trimester as well.

118 At the age of 49 she again became pregnant of a twin pregnancy after oocyte  
119 donation and IVF in another clinic in Belgium. She now seemed to be mentally more  
120 stable. Antenatal visits were at a Dutch clinic, and the pregnancy developed  
121 uneventful. At a gestational age of 37 weeks her blood pressure had risen from  
122 110/60 to 125/80 mmHg. At 38 weeks labour was induced for elective reasons and

123 the woman delivered a healthy boy and girl, at the age of 50. Shortly postpartum her  
124 blood pressure had risen to 170/100 mmHg. She complained of nausea and  
125 vomiting. No diagnostic tests, however, were performed and no antihypertensive or  
126 anticonvulsant therapy was initiated. Nine hours later she was found unconscious in  
127 bed with a tongue bite. Magnesium sulfate was initiated, but she had two more  
128 convulsions. Blood results showed signs of HELLP-syndrome. Following the  
129 eclamptic fit she was somnolent and disoriented, with a bloodpressure of 140/85  
130 mmHg. After 24 hours CT-scan showed occipital haemorrhage and cerebral oedema.  
131 She was transferred to the Intensive Care Unit. After a few hours the Glasgow Coma  
132 Scale deteriorated and a midline shift was visible at the CT scan. Treatment was  
133 stopped because of brain death and she died. Her husband was left behind with four  
134 children.

135

#### 136 Discussion

137 This woman died from eclampsia, after she had a multiple pregnancy at advanced  
138 age after oocyte donation IVF. She insisted to have this treatment and being denied  
139 IVF in her own country, The Netherlands, she had it performed abroad. The woman  
140 had hypertension and pre-eclamptic complaints, but was not managed with  
141 antihypertensive medication or magnesium sulphate.

142 We feel that even the first oocyte donation for this woman could be criticised, but are  
143 astonished that doctors did institute such rigorous treatment for the second time, at  
144 the age of 49, after the first pregnancy resulting from oocyte donation was chosen to  
145 be terminated. The availability of advanced reproductive technology, especially for  
146 the richer women in society, may create a new, unnecessary, group at risk in high  
147 income countries for severe maternal morbidity as well as mortality. Women should  
148 be counselled intensively about the risks involved.

149 IVF, twin pregnancy and advanced age are all risk factors for pre-eclampsia, one of  
150 the five major causes of maternal death worldwide, and the leading cause of  
151 maternal mortality in The Netherlands.

152 IVF-pregnancies are associated with more obstetric complications than naturally  
153 conceived pregnancies.<sup>6</sup> Källén et al found higher risks of pre-eclampsia (OR 1.63;  
154 95% CI 1.53-1.74), placental abruption (OR 2.17; 95% CI 1.74-2.72) and postpartum  
155 haemorrhage (OR 1.4; 9% CI 1.38-1.50) in women being pregnant after IVF-  
156 treatment.<sup>7</sup> Venn et al reported an increased risk of maternal mortality in IVF

157 pregnancies: 25.7 per 100.000 pregnancies compared to 10.9 in non-IVF  
158 pregnancies.<sup>8</sup>

159 Whether oocyte donation adds an additional risk to the higher risks of obstetric  
160 complications in IVF-pregnancies remains controversial, but most studies indicate an  
161 additional risk. Söderström-Anttila et al compared obstetric outcome of pregnancy  
162 after oocyte donation with pregnancies after standard IVF. In singleton pregnancies  
163 they observed 29% (12/41) pregnancy-induced hypertension in the first group versus  
164 12% (8/68) in the other group ( $P < 0.05$ ). Also, the caesarean section rate was  
165 higher: 57% (29/51) in the group with oocyte donation versus 37% (36/97) in the  
166 standard IVF group.<sup>9</sup>

167 Henne et al found an increased risk of preterm labour, pre-eclampsia and caesarean  
168 delivery (after controlling for age and multiple gestations) in recipients of donor  
169 oocytes versus women of advanced age with autologous oocytes.<sup>10</sup> Wiggins et al  
170 found 26% (6/23) pregnancy-induced hypertension in the group with donor egg IVF  
171 as compared to 8% (1/12) in the group with standard IVF. For nulliparous women this  
172 difference was even more significant with 37% (13/35) in the donor egg IVF group  
173 and 8% (3/37) in the group with standard IVF (OR 7.1; 95% CI 1.4-36.7).<sup>11</sup> Sauer et  
174 al reported in their cohort study in 37.8% (28/74) of pregnancies after oocyte  
175 donation obstetrical complications.<sup>12</sup> This was also seen in the cohort of Abdalla, with  
176 a high risk of pregnancy induced hypertension and postpartum haemorrhage.<sup>13</sup>

177 Krieg et al also compared 71 donor oocyte pregnancies with 108 IVF pregnancies  
178 using autologous oocytes at advanced maternal age. They found no differences in  
179 incidence of hypertensive disorders, gestational diabetes or mode of delivery after  
180 controlling for multifetal gestation, gestational age at delivery and maternal age.<sup>14</sup>

181 Women being pregnant at advanced age have an increased risk for pre-eclampsia  
182 and gestational diabetes.<sup>15</sup> Advanced age is also an independent risk factor for  
183 caesarean delivery (OR 2.3, 95% CI 1.1-4.8).<sup>16</sup> Paulson et al reported an incidence  
184 of pre-eclampsia of 25% (10/40), being 60% (6/10) in women older than 55 years.  
185 The incidence of gestational diabetes was 17.5% (7/40), with an incidence of 40% in  
186 women older than 55 years (4/10).<sup>17</sup> The doctors offering IVF procedures should be  
187 aware of the risks named above.

188 Also, important moral and social questions should receive attention. Patient  
189 autonomy is an important ethical principle in management, but we feel that there are  
190 limits to this. Doctors are also bound to the principle of 'not doing harm' and this

191 principle was at stake in our case.<sup>18</sup> The discussion whether women over the age of  
192 50 should have children is still not closed.<sup>2,3</sup> Landau even reports an increase, rather  
193 than a decrease, of human suffering due to the promise of post-menopausal  
194 pregnancy with unlimited fertility.<sup>19</sup> Doctors do have the right to refuse to give medical  
195 treatment such as IVF-treatment. If it is decided to offer this treatment to a woman at  
196 advanced age, the doctor should counsel women intensively about the risks before  
197 such treatment is started. When provided they remain responsible for the wellbeing of  
198 their patient.

199

## 200 Conclusions

201 The discussion whether women at advanced maternal age should become pregnant  
202 is still not closed. Doctors, however, have the right to refuse to perform such  
203 treatment. Pregnancies at advanced maternal age after oocyte IVF-treatment have  
204 increased risks of obstetrical complications. We should be aware of these risks and  
205 counsel patients accordingly.

206

206 Consent:

207 Written informed consent was obtained from the husband of the patient for  
208 publication of this case report and any accompanying images. A copy of the written  
209 consent is available for review by the Editor-in-Chief of this journal.

210

211 Competing interests:

212 The authors declare that they have no competing interests.

213

214 Financial interests:

215 There was no funding.

216

217 Authors contributions:

218 All authors have made substantive intellectual contributions to this study. We all  
219 contributed to the conception of the article and to the acquisition and analysis of the  
220 case. All authors read and approved the final manuscript.

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