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1 **Feticide in second- and third-trimester termination of pregnancy for fetal**
2 **anomalies: results of a national survey**

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26 Bulleted Statement:

27 What's already known about this topic?

28 Although the WHO recommends feticide for elective termination of pregnancy (TOP)
29 after 20 weeks, in France, as in most other European countries, there is no legal
30 obligation to perform this procedure in the framework of TOP for fetal anomalies.

31 What does this study add?

32 First study on a national scale of feticide in the setting of termination of pregnancy for
33 fetal anomalies showing that most TOP performed after 22 weeks in France are
34 associated with feticide, usually after fetal anesthesia.

35 Data availability statement: The data that support the findings of this study are
36 available from the corresponding author upon reasonable request.

37 Ethics Approval: N/A. This study consisted on evaluation of medical protocols. It does
38 not involve any patients or personal staff data.

39

40

41

42 **Abstract**

43 Objective: to conduct an audit of the practice of feticide in second- and third-trimester
44 termination of pregnancy for fetal anomalies (TOPFA) in prenatal diagnosis (PD)
45 centers in France.

46 Results: A questionnaire was sent out to the 49 French PD centers and completed by
47 39/49 centers. 5350 TOPFA were performed. The gestational age after which feticide
48 was performed was 20 weeks in 2 centers (5%), 22 weeks in 28 centers (72%), 23
49 weeks in 4 centers (10%), and 24 weeks in 5 centers (13%). Fifteen of 39 centers
50 reported that feticide was not performed in all cases, because of a fetal abnormality

51 associated with a high probability of rapid neonatal death (13 centers), **pregnant**
52 **woman's** refusal (11 centers), and technical impossibility of performing feticide (1
53 center). Feticide was done using xylocaine in 38 of the 39 centers and using KCl in
54 the remaining center. All but one of the centers before feticide used fetal anesthesia.
55 Feticide was done on the day of induction of labor in 35/39 centers (90%), after
56 maternal epidural analgesia in 33 centers, or after maternal subcutaneous local
57 anesthesia in 2 centers. Feticide was done the day before induction of labor in 2
58 centers.

59 Conclusion: In France, most TOPFA performed in second- and third trimester are
60 associated with feticide, which is most often done after fetal anesthesia.

61

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66 the responding centers.

67 Keywords: termination of pregnancy for fetal anomalies, feticide, second- and third
68 trimester, fetal analgesia.

69

70 Contribution: JMJ, PM, AL designed the study and interpreted the data. PM, JMJ, AB
71 interpreted the data and wrote the article.

72 **Introduction**

73 The growth of prenatal diagnosis over the last 3 decades has greatly
74 increased the rate of prenatal detection of fetal anomalies. This rate varies among
75 European countries, but ranges between 30 and 80% according to data from the
76 European registers¹⁻³. Certain fetal anomalies can lead to the organization of specific
77 perinatal management, sometimes with the possibility of specific fetal therapy^{4,5}. In
78 most European countries, termination of pregnancy for fetal anomalies (TOPFA) may
79 be requested by the parents when the anomalies are severe, considered incurable,
80 and associated with a high risk of severe disability. However, the legislative
81 provisions, notably concerning a time limit beyond which TOPFA is no longer
82 authorized, vary from one country to another.

83 French law authorizes TOPFA when there is a strong probability that the **fetus**
84 has a particularly serious anomaly recognized as incurable at the time of diagnosis⁶.
85 In France, there is no gestational age cut-off. When a **pregnant woman** opts for
86 TOPFA, two fetal medicine specialists who are members of a prenatal diagnosis (PD)
87 center must attest that the fetal anomaly is covered by the legal provisions in force.

88 Although the World Health Organization recommends feticide for elective
89 termination of pregnancy after 20 weeks, in France, as in most other European
90 countries, there is no legal obligation to perform this procedure in the framework of
91 TOPFA. Several studies have examined the technical aspects of feticide, notably
92 concerning the lethal substances used and their route of administration, ie, fetal or
93 intra-amniotic injection⁷⁻¹¹. Some studies have examined the psychological
94 experiences of both the parents and the healthcare professionals involved¹²⁻¹⁴.
95 Expert opinions have also been formulated concerning the ethical issues associated
96 with whether or not feticide should be performed in the setting of TOP, whatever the

97 indications. In contrast, no study to date has reported the incidence of feticide in the
98 setting of TOPFA. Such an overview of the practice of feticide could serve as a basis
99 for reflection by healthcare professionals and governmental decision-makers on
100 standardization of practices and on the organization of TOPFA.

101 The main objective of our study was to describe the practice of feticide in
102 TOPFA during the second and third trimesters of pregnancy in (PD) centers in
103 France. The secondary objective was to study methods of feticide and why it may not
104 be performed.

105

106

107 **Material and methods**

108 The Fédération Française des Centres Pluridisciplinaires de Diagnostic
109 Prénatal conducted a national questionnaire survey in 2018 concerning TOPFA
110 performed in 2017. The questionnaire was drawn up by a committee appointed by
111 the Federation that comprised 8 center coordinators representative of physicians
112 involved in TOPFA, taking into account the gender and age of the physicians and the
113 number of TOPFA performed in their center, while ensuring a balanced geographical
114 distribution throughout France. This questionnaire, which was approved by means of
115 a consensus of all 8 coordinators, was limited to feticide in a setting of TOPFA, and
116 excluded termination of pregnancy for maternal reasons (life-threatening to **pregnant**
117 **woman**). The questions related notably to whether or not feticide was universally
118 performed, the gestational age at which feticide was practiced, the timing of feticide
119 in TOPFA, and the technical modalities of feticide: site of injection, use of prior fetal
120 anesthesia, type of lethal substance used. The questionnaire also included questions
121 on the existence of a protocol at the center, the medical resources available for

122 ultrasound-guided termination of pregnancy, and the number of TOPFA done at the
123 centers during the previous year and reported to the Agence de la biomédecine, the
124 public body charged with oversight of the CPNs. Lastly, the questionnaire recorded
125 the reasons why some centers do not practice feticide universally. After the
126 questionnaire was sent out, two follow-ups were sent over a period of 6 months. A
127 member of the administrative staff of the Fédération Française des Centres
128 Pluridisciplinaires de Diagnostic Prénatal collected and anonymized the
129 questionnaire answers.

130

131 **Results**

132 Of 49 PD centers contacted, 39 completed the questionnaire (80%). A total of
133 5350 TOPFA were done by these 39 centers in the year corresponding to the survey
134 (2017). According to data collected by the Agence de la biomédecine for this same
135 year, a total of 6938 TOPFA were reported in France as a whole. Our survey
136 therefore covered 77% of the TOPFA performed. The median [range] number of
137 TOPFA performed in these centers was 121 [36-339]. The gestational age after
138 which feticide was performed was 20 weeks in 2 centers (5%), 22 weeks in 28
139 centers (72%), 23 weeks in 4 centers (10%), and 24 weeks in 5 centers (13%). In
140 each center, the median (extreme) number of experienced operators with ability to
141 perform feticide was 4 (1-8). Of the 39 centers, 24 (62%) reported systematic use of
142 feticide beyond the gestational age chosen by the center (Table 1). Fifteen of the 39
143 centers reported non-systematic use of feticide, the reason being a fetal anomaly
144 with a strong probability of rapid neonatal death (13 centers), refusal by **the**
145 **pregnant woman** (11 centers), and a technical impossibility of performing feticide (1
146 center). In all, 23 TOPFA were performed without feticide during the survey period,

147 but this information was not provided by 17/39 centers. The lethal substance used for
148 feticide was 1% or 2% xylocaine in 38/39 centers and KCl in one center. All but one
149 centers used fetal anesthesia before feticide. The center that did not use fetal
150 anesthesia universally performed feticide by intracardiac injection of the lethal
151 substance. Fetal anesthesia was achieved by injection of fentanyl or pentothal or of a
152 mixture of the two, at a dose adapted to the ultrasound estimate of fetal weight. In 30
153 centers (82%), fetal anesthesia was routinely achieved by ultrasound-guided injection
154 into the umbilical vein (Table 2). At the other centers, the injection site was
155 intracardiac or subcutaneous. Feticide was done on the day of induction of labor in
156 35/39 centers (90%), after maternal epidural analgesia in 33 centers, and after
157 maternal subcutaneous anesthesia in 2 centers. Feticide was done the day before
158 the induction of labor, after local maternal anesthesia, in 2 centers (5%).

159 All CPNs reported that they worked in a network with maternity units outside
160 the tertiary institution of which they are a part, with the possibility of organizing
161 TOPFA in these maternity units. However, 19/39 centers (49%) reported that TOPFA
162 were only performed in the maternity unit of the tertiary institution to which the CPN
163 was attached when the feticide was done, because the other maternity units did not
164 have staff with the technical skills required for this ultrasound-guided procedure
165 (Table 1). All but one of the CPNs that completed the questionnaire had the medical
166 resources required for emergencies 24/7 in the case of unexpected labor when
167 TOPFA is scheduled with feticide.

168

169

170 **Discussion**

171 Ours is the first French study describing of the use of feticide in TOPFA. Its
172 results suggest that in France most TOPFA during the second and third trimesters of
173 pregnancy are practiced after fetal anesthesia and feticide. In most centers that
174 completed our questionnaire, feticide is almost always done after 22 weeks of
175 gestation, and very few TOPFA are organized without feticide after 22-24 weeks.

176 While the World Health Organization recommends feticide for late TOP, in
177 France, unlike other countries, there is no legal obligation to perform feticide. Yet,
178 feticide appears to be ethically justified when it prevents **neonatal demise**
179 **associated with a risk of suffering or pain**¹⁵⁻¹⁸. Studies in the literature on late
180 TOP concern in large part second-trimester TOP, and notably TOP performed
181 according to the wishes of the parents, in the context of a normal pregnancy. These
182 TOP are authorized in several countries up until 24 weeks, as in the UK. Given that
183 almost all these TOP are performed using a surgical technique, the question of fetal
184 survival does not arise. The context of TOP for fetal anomalies is different because
185 TOP is legal after 22 weeks, notably in several European countries. In TOPFA, in
186 most cases, it may be helpful to perform a postmortem examination of the fetus to
187 define the fetal disease and to facilitate genetic counseling for subsequent
188 pregnancies. It is against this backdrop of induction of labor that feticide is posed.
189 However, there is the question of its acceptability to **pregnant women** and to
190 healthcare professionals. Most studies of feticide have focused on its technical
191 aspects: route of fetal injection, type of lethal substance used, and so forth⁷⁻¹⁰. These
192 studies mainly concentrated on maternal risks. It was thus shown that injection in the
193 umbilical vein involved the least risk to the **pregnant woman**⁷. It seems that
194 xylocaine is associated with the lowest maternal risk and achieves fetal asystole in
195 most cases⁸. Some authors consider that intracardiac injection is surer, and in some

196 cases failure of injection in the umbilical cord has led to the birth of live infants^{11,19,20}.
197 It is possible, moreover, that such failures are underreported in the literature. Even if
198 exceptional, such failures expose the parents, and also the healthcare professionals
199 delivering these neonates, to the risk of psychological trauma. To avoid such
200 situations, it seems prudent to recommend testing for fetal asystole using ultrasound,
201 at least 10-15 minutes after feticide by injection in the umbilical cord.

202 Although little discussed in the literature, feticide requires experience of
203 invasive, ultrasound-guided procedures. This may be a limiting factor in the
204 organization of some teams. In our study, 19/39 centers reported that TOPFA
205 requiring feticide was performed in the maternity unit of the PD center because other
206 maternity units in the region had no physician able to perform the procedure.
207 Interestingly, the intra-amniotic injection of digoxin in TOP has been reported to
208 achieve fetal demise within about 24 hours¹⁰. This injection is technically simpler than
209 injection in the umbilical cord or intracardiac injection. In a recent study, this
210 technique achieved fetal demise in up to 93% of reported cases¹⁰. The risk of failure
211 seemed to be greater in the case of maternal obesity. The results of this study are
212 interesting as they could argue in favor of easier access to this procedure, notably for
213 couples living far from tertiary centers. However, the precise time lapse between
214 intra-amniotic injection and fetal death is unknown. Our study shows that most
215 French CPNs perform fetal anesthesia before feticide in accordance with the
216 guidelines of the French College of Obstetricians and Gynecologists²¹. Interestingly,
217 fetal pain is little considered in studies on late TOP.

218 The strength of our study is that fetal medicine in France is organized in
219 approved specialized centers, which were set up following the bioethics laws of 1994.
220 At the time of our study, there were 49 such centers throughout mainland France and

221 French overseas territories. The expert members of these centers are accredited by
222 the Agence de la biomédecine, the public body that has oversight of the running and
223 organization of these 49 centers. This facilitates centralization of the organization of
224 TOPFA. French legislation imposes no limit on the term of gestation for TOPFA when
225 there is a strong probability that the unborn child has a serious disease
226 acknowledged to be incurable, at the time of diagnosis. Even though legal provisions
227 differ from one country to another, late TOPFA is authorized in several countries,
228 notably in Europe.

229 The main limitation of our study is that not all the PD centers contacted
230 completed our questionnaire. Those that did, however, accounted for 77% of TOPFA.
231 In addition, our figures are in line with the proportion of feticides reported in the
232 EPIPAGE cohort, which studied TOP prevalence and indications in 7804 premature
233 births (between 22 weeks and 31 weeks plus 6 days)²². In this study, for TOPFA, the
234 rate of feticide was 80% at 24 weeks of gestation and over 90% from 26 weeks.
235 Moreover, among the 11/49 centers that failed to respond in our study, there was no
236 regional or workload disparity that could have introduced bias. Another limitation of
237 our survey is that it was self-report in nature, which could be a source of bias.
238 However, most of the information corresponds to data that must be reported every
239 year to the Agence Nationale de la Biomédecine, which regularly conducts quality
240 controls of transmitted data.

241

242 Ours is the first study on a national scale of feticide in the setting of TOPFA. It
243 shows that most TOPFA performed most TOPFA performed in second- and third
244 trimester are associated with feticide, usually after fetal anesthesia administered by
245 injection in the umbilical cord.

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317 **Table 1:** Organization of feticide during second- and third-trimester termination of
 318 pregnancies among the 39 prenatal diagnosis centers
 319
 320

	Yes
Is feticide done universally?	24/39
Does your center's organization allow "emergency" feticide 24/7 (eg, in the case of spontaneous labor)?	
In the maternity unit housing your CPD	38/39
In another maternity unit of the network of your CPD	22/39
Does the indication for feticide in TOP imply management of the patient outside her original maternity unit?	19/39
Is fetal anesthesia always done before feticide?	38/39

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 322
 323

324 **Table 2:** Site of injection of the fetal anesthesia and lethal substance among the 39
325 prenatal diagnosis centers
326
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	Umbilical cord	Intracardiac	Subcutaneous	Depending on the conditions
Site of injection of the fetal anesthesia	31/38	2/38	0/38	3/38
Site of injection of the lethal substance	9/39	3/39	N/A	27/39

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