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Indications leading to termination of pregnancy between 22+0 and 31+6 weeks of gestational age in France: A population-based cohort study

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► To cite this version:

Isabelle Monier, Nathalie Lelong, Pierre-Yves Ancel, Alexandra Benachi, Babak Khoshnood, et al.. Indications leading to termination of pregnancy between 22+0 and 31+6 weeks of gestational age in France: A population-based cohort study. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 2019, 233, pp.12-18. 10.1016/j.ejogrb.2018.11.021 . hal-04511560

HAL Id: hal-04511560

<https://hal.science/hal-04511560>

Submitted on 26 Mar 2024

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1 **Indications leading to termination of pregnancy between 22⁺⁰ and 31⁺⁶ weeks of**
2 **gestational age in France: a population-based cohort study**

3

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24 **Word count:** Abstract: 258 Main text: 2533

25

26 **Abstract**

27

28 **Indications leading to termination of pregnancy between 22⁺⁰ and 31⁺⁶ weeks of**
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33 **Objective:** To estimate the prevalence and indications of terminations of pregnancy
34 (TOP) between 22⁺⁰ and 31⁺⁶ weeks of gestational age in France and to examine the
35 characteristics of women by indication of TOP.

36 **Study design:** From the EPIPAGE 2 population-based cohort study of preterm births
37 in France in 2011, we selected 5009 singleton live births, stillbirths and TOP that
38 occurred between 22 and 31 weeks. We estimated the proportion of TOP by
39 gestational age. We then classified terminations by indications into 4 categories: fetal
40 anomalies (TOPFA), preterm premature rupture of the membranes (PPROM),
41 maternal conditions and fetal growth restriction (FGR). We also classified TOPFA by
42 type of anomaly. Maternal characteristics were compared between TOPFA and TOP
43 for maternal or fetal conditions without congenital anomaly.

44 **Results:** 23.1% of all births and 54.3% of stillbirths were terminations. The proportion
45 of terminations was 36.9% of all births at 22 weeks, 50.2% at 24 weeks and <10% at
46 30-31 weeks. 85.8% of terminations were for fetal anomaly, 4.4% for PPRM, 6.1%
47 for maternal complications and 3.7% for severe FGR. Compared to women with a
48 TOPFA, those with a termination for maternal or fetal conditions were more often
49 nulliparous, single, African, obese, smokers and covered by non-standard insurance
50 for women in socially deprived circumstances.

51 **Conclusion:** In France, there is a high proportion of TOP of which 14% are for
52 indications other than congenital anomalies. Because rates of terminations have an
53 impact on very preterm birth and perinatal mortality rates, studies on pregnancy
54 outcome should report all terminations, not only those for congenital anomalies.

55 **Key-words:** terminations of pregnancy, preterm births, stillbirths, EPIPAGE 2

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76 **Introduction**

77 Terminations of pregnancy (TOP) are pregnancies that end to fetal deaths due to
78 multiple conditions, most often congenital anomalies if the child is expected to have a
79 risk of serious handicap, or pregnancy complications if there is substantial risk for the
80 mother's life.(1) Most TOP are carried out at early gestational ages.(2,3) In some
81 countries, terminations are also possible at later gestational age, after 21 completed
82 weeks of gestational age (GA). These differences in policies and practices relating to
83 TOP can affect estimates of perinatal mortality rates, if TOP are included in perinatal
84 mortality statistics, and can influence evaluations of medical practices and survival of
85 very preterm births.(4–7) A study on births between 22 and 31 weeks GA showed
86 that more than 20% of stillbirths were TOP in many European regions and this
87 proportion reached more than 40% in regions from Italy and France.(6) Therefore,
88 information on the prevalence of TOP by gestational age and indication is important
89 for international comparisons of perinatal health indicators. However, national-level
90 data on TOP are scarce and most existing studies have focused on TOP for
91 congenital anomalies,(8–13) whereas TOP are also carried out for other pregnancy
92 complications.(14–16)

93

94 In a recent study, France reported the highest proportion of terminations among
95 stillbirths at or after 22 weeks of gestation in Europe.(5) This study used aggregate
96 data and was not able to describe the medical decision-making processes leading to
97 the high number of TOP in France. Therefore, we aimed to estimate the prevalence
98 of TOP among very preterm births, describe the indications of terminations and study
99 the maternal characteristics according to the indication for termination using a
100 population-based study of all births from 22 to 34 weeks GA in France in 2011.

101

102 **Methods**

103

104 *Study design and population*

105 The EPIPAGE 2 study is a national population-based prospective cohort of infants
106 born between 22⁺⁰ and 34⁺⁶ weeks GA in 25 French regions in 2011 (N=7804).(17)
107 All live births, stillbirths and TOP were included during three different periods
108 according to gestational age at birth: 8 months for births between 22-26 weeks GA, 6
109 months for those between 27-31 weeks GA and 5 weeks for those between 32-34
110 weeks GA. The study population included 5009 singleton births between 22⁺⁰ and
111 31⁺⁶ weeks GA in 415 maternity units. Multiple pregnancies were excluded because
112 the indications for TOP can differ from singleton pregnancies. We also excluded
113 births between 32 and 34 weeks GA because of the short recruitment period for
114 these births.

115

116 *Variables*

117 Data were abstracted from medical charts using a standardized questionnaire. TOP
118 were classified by medical indication into 4 exclusive and hierarchical classes: 1)
119 fetal anomaly (TOPFA), 2) preterm premature rupture of the membranes (PPROM)
120 defined as the rupture of membranes at least 12 hours before the beginning of labor,
121 or anomaly of amniotic fluid, 3) maternal conditions including pregnancy
122 complications related to diseases such as hypertensive and psychiatric disorders and
123 4) severe and isolated fetal growth restriction (FGR) with no hypertensive disorder
124 and no apparent congenital anomaly.

125

126 We classified TOPFA according to the classification of multiple congenital anomaly
127 (MCA) algorithm defined in the European Surveillance of Congenital Anomalies
128 (EUROCAT) guidelines.(18) Congenital anomalies were classified into 8 exclusive
129 groups following this order: 1) chromosomal anomalies, 2) genetic syndromes, 3)
130 infections during pregnancy associated with fetal abnormalities (mainly
131 toxoplasmosis and cytomegalovirus infections), 4) isolated neural tube defects, 5)
132 isolated heart cardiac defects, 6) isolated renal disorders, 7) isolated other anomalies
133 (eye, ear, face and neck anomalies, limb reduction defects, oro-facial clefts, digestive
134 system, genital anomalies) and 8) potential multiple anomalies defined as two or
135 more anomalies.(19) We created a ninth group for fetal anomalies with no
136 information on the type of anomaly (or insufficient information on the type of anomaly
137 to permit classification).

138

139 Maternal characteristics included maternal age, parity, family situation (cohabiting or
140 single), country of birth, medical insurance, body mass index (BMI) before pregnancy
141 and smoking during pregnancy. We used the type of medical insurance as an
142 indicator of underprivileged situation: women have a non-standard insurance, if they
143 are undocumented or have very low income.

144

145 *Prenatal care and management of terminations in France*

146 In France, an ultrasound is recommended at each trimester of pregnancy for women
147 with no complication including an ultrasound screening for congenital anomalies
148 between 22 and 24 weeks GA.(20) Terminations are allowed at any gestational age
149 for congenital anomalies, medical conditions or social reasons if the continuation of
150 the pregnancy would lead to risk for women's health or if the child is expected to

151 have a “serious illness, recognized as incurable at the time of diagnosis”.(1)
152 Decisions for pregnancy terminations must be approved by a multidisciplinary
153 committee for prenatal diagnosis.

154

155 *Statistical analysis*

156 We estimated the proportion of TOP with 95% confidence interval by gestational age,
157 as a percentage of all births and as a percentage of stillbirths. For these calculations,
158 all births included live births, TOP and spontaneous fetal deaths, and stillbirths
159 included TOP and spontaneous fetal deaths. We also reported the proportion of
160 feticides by gestational age. Then, we compared maternal characteristics between
161 TOP for congenital anomalies and TOP for maternal conditions or FGR, using Chi
162 square tests. Finally, we estimated the percentage of all TOPFA by type of fetal
163 anomaly. In order to compare our results with other studies, we also reported the
164 percentage of TOPFA between 22 and 26 weeks and between 27 and 31 weeks GA.

165

166 Percentage were weighted to account for the 9-week longer recruitment period for
167 births at 22-26 weeks GA. Analyses were performed using STATA 13.0 software
168 (StataCorpLP, College Station, TX, USA).

169

170 **Results**

171 Among the 5009 births between 22⁺⁰ and 31⁺⁶ weeks GA, there were 1266
172 terminations (23.1%). (Table 1) The percentage of TOP was 36.9% (95% CI: 32.6-
173 41.3) at 22 weeks; it increased to 50.2% (95% CI: 45.9-54.4) at 24 weeks GA and
174 then decreased to less than 10% at 30-31 weeks GA. The percentage of TOP among
175 stillbirths was 54.3% and it varied by gestational age from 35.9% to 70.4%. A feticide

176 was recorded in medical charts for 78.2% of terminations: 47.9% (95% CI: 40.5-55.5)
177 at 22 weeks, 58.6% (95% CI: 51.7-65.1) at 23 weeks and more than 90% after 26
178 weeks. For instance, at 22 weeks GA, no mention of feticide was found for 48.8% of
179 TOP for congenital anomalies, 60.9% of TOP for PPROM, 47% of TOP for maternal
180 indications and 100% of TOP for severe FGR (n=4).

181

182 Table 2 presents the percentage of TOP by medical indication and gestational age.
183 Overall, 85.8% of TOP were carried out for congenital anomaly, 4.4% for PPROM or
184 anomaly of amniotic fluid, 6.1% for maternal complications and 3.7% for severe FGR.
185 At 22-23 weeks GA, 78.4% of terminations were for congenital anomalies and this
186 percentage increased with gestational age to 97.5% at 30-31 weeks GA. At these
187 GA, the percentages of terminations for maternal conditions or FGR were 9.3% and
188 1.3% respectively. At 22 and 23 weeks of gestation, the 9 fetuses born after TOP
189 carried out for isolated FGR had severe FGR with birthweight ranging between 110
190 and 350 grams.

191

192 Table 3 compared terminations for congenital anomaly to those for maternal
193 indications or FGR. Women with terminations for maternal indications or FGR were
194 often nulliparous (52.7% vs 40.8%, $p=0.003$), single (11.8% vs 4.7%, $p<0.001$),
195 African (18.3% vs 7.6%, $p<0.001$), obese (16.6% vs 9.8%, $p=0.012$), smokers
196 (22.9% vs 15.2%, $p=0.011$) and covered by non-standard medical insurance for
197 pregnant women in socially deprived circumstances (12.1% vs 7.5%, $p=0.049$). No
198 difference between the groups was found for maternal age.

199

200 Among TOP for fetal anomaly between 22 and 31 weeks, 22.6% (95% CI: 20.2-25.2)
201 were for chromosomal abnormalities, 21.9% (95% CI: 19.5-24.5) for isolated neural
202 tube defects, 13.8% (95% CI: 11.8-16.0) for isolated cardiac defects and 11.5% (95%
203 CI: 9.7-13.6) for multiple anomalies. (Table 4) Among chromosomal anomalies,
204 44.2% were for Down's syndrome (Trisomy 21), 25.8% for Edward syndrome
205 (Trisomy 18), 8.4% for Patau syndrome (Trisomy 13) and 21.6% for other
206 chromosomal anomalies. Less than 10% of TOP for congenital anomaly were for
207 genetic syndromes, infections or other isolated anomalies. These distributions were
208 similar for TOPFA between 22 and 26 weeks and between 27 and 31 weeks GA.

209

210 **Comment**

211

212 *Main findings*

213 In France in 2011, terminations represented almost one quarter of all singleton births
214 and half of stillbirths between 22 and 31 weeks GA. Most terminations were carried
215 out for fetal anomaly, mainly for chromosomal abnormalities and isolated neural tube
216 defects. About 15% of terminations were for maternal and fetal pregnancy
217 complications unrelated to congenital anomalies but these indications were rare after
218 28 weeks GA. Women who had a termination for maternal or fetal pregnancy
219 complications were more often nulliparous, obese, African, smokers and covered by
220 non-standard medical insurance compared to those who had a termination for
221 congenital anomaly.

222

223 *Strengths and limitations*

224 The principal strength of our study is its population-based prospective design. We
225 included all TOP between 22 and 31 weeks GA in 25 out of 26 French regions. The
226 inclusion of all eligible births was ascertained by members of the regional
227 coordinating committee in all maternity units.(17) Further, we included terminations
228 for other reasons than congenital anomalies and we studied maternal characteristics
229 related to these terminations, whereas most previous studies have focused only on
230 terminations for congenital anomalies.(8–13)

231

232 Our study also has some limitations. We did not include terminations at 32-34 weeks
233 GA because of the shorter recruitment period and consequently the small number of
234 cases (N=15) and we did not have any information on terminations after 34 weeks.
235 Additionally, there may be some classification errors: for instance spontaneous
236 intrauterine deaths classified as TOP if scheduled TOP ended in fetal death before
237 termination,(21) or conversely, some terminations being coded as stillbirths.

238

239 *Interpretation*

240 We calculated that 23.1% of very preterm singleton births and 54.3% of stillbirths
241 were terminations. These high proportions corroborate results from previous studies.
242 For instance in 2003, in one French region, these proportions were 21.5% and 52.5%
243 respectively whereas less than 6% of very preterm births were terminations in two
244 regions in UK.(6) More generally, there is a high proportion of TOP regardless of
245 gestational age in France, when compared to other European countries,(2) and this
246 is especially true at low gestational ages.(5) Several factors contribute to this
247 situation. France has an active policy of screening for congenital anomalies resulting
248 in a high proportion of TOP among fetuses with congenital anomaly. For instance,

249 between 2002 and 2004, 96% and 98% of pregnancies diagnosed with a Down's
250 syndrome and neural tube defects respectively ended in a termination.(7) In addition,
251 terminations are allowed at any gestational age and this makes possible to wait for
252 results of additional investigations to provide the best prognostic information to
253 parents for their decision.(1) Finally, the second-trimester screening ultrasound is
254 planned at 22-24 weeks, as opposed to before 20 weeks in many other countries,
255 leading to a shift on the timing of terminations in France.

256

257 In our study, a feticide was not mentioned in medical charts for 48% of terminations
258 at 22 weeks and 40% at 23 weeks of gestation. Some terminations without feticide
259 may be explained because of absence of beating of fetal heart before the onset of
260 labor or because some parents do not want a feticide. The information on the feticide
261 may also have been forgotten in some medical files. In addition, there is no
262 recommendation for feticide in France. This difference in medical guidelines may
263 explain that no feticide was reported for 18% of terminations between 22 and 26
264 weeks in the EPICure study compared to 27.5% in our study.(21) Nevertheless, it
265 seems that a feticide is routinely offered for terminations after 22 weeks GA in
266 France.(22)

267

268 We found that women who had a termination for maternal or fetal compromise were
269 different to those who had a termination for congenital anomaly. They were more
270 often nulliparous, obese, African, with non-standard medical insurance and smokers.
271 These characteristics are well-known risk factors for vascular diseases including pre-
272 eclampsia and FGR.(23–25) We did not find any association with older maternal age
273 which is known to be a major risk factor for hypertensive disorders during

274 pregnancy.(26) This result can be explained by the use of terminations for congenital
275 anomaly as a comparison group, as older women also have an increased risk of
276 having a fetus with a congenital anomaly.(27)

277

278 Chromosomal anomalies were the most frequent indication for terminations among
279 all TOPFA (22.6%). Most of these anomalies were trisomies in our study as in
280 UK(21) and more generally in Europe,(8) although there is an active policy of
281 antenatal screening for Down's syndrome resulting in terminations before 22 weeks.
282 We also found that isolated neural tube defects were a frequent indication. Between
283 22 and 26 weeks, 22.1% of terminations were carried out for isolated neural tube
284 defects in our study and 31.2% in the EPICure study.(21) Several randomized
285 controlled trials have demonstrated the efficacy of folic acid supplementation before
286 pregnancy for the reduction of neural tube defects.(28) However, a population-based
287 study showed that the prevalence of neural tube defects has not decreased in
288 Europe during the last two decades.(29) This may be explained by difficulties in the
289 implementation of folic acid supplementation, despite national recommendations
290 issued in each country. In France, only 15% of pregnant women had folic acid before
291 pregnancy in 2010.(30) In contrast, there was a decrease in the live birth prevalence
292 of neural tube defects, as a result of prenatal diagnosis and terminations.(29)

293

294 In our study, we estimated that 15% of terminations were for maternal or fetal
295 conditions. Maternal reasons were responsible of 6% of terminations. In 2003, 5% of
296 terminations among very preterm births were for maternal reasons in one French
297 region.(6) Two studies focusing on terminations for maternal conditions showed that
298 maternal hypertensive disorders were the most frequent reason for these

299 terminations.(14,15) We also estimated that 3.7% of terminations were for severe
300 isolated FGR. A study using the EPIPAGE 2 data showed that 11.6% of pregnancies
301 suspected with early-onset FGR without a fetal anomaly resulted in terminations
302 between 22 and 31 weeks and this proportion was higher when FGR was detected
303 before 26 weeks of gestation.(31)

304

305 A high proportion of late terminations leads to increased preterm birth and stillbirth
306 rates.(5,6,32) Less is known about the impact of late terminations on indicators of
307 newborn and infant health, but some studies have shown an effect of policies and
308 practices of terminations on mortality rates. Studies in Canada suggested that the
309 increase in terminations for congenital anomaly between 2000 and 2010, especially
310 at 20-21 weeks, led to a decrease in neonatal mortality rates and the prevalence of
311 live-born infants with congenital anomalies.(4,12) Studies from countries where
312 terminations are restricted also report higher rates of infant deaths associated with
313 congenital anomalies.(6,33) These effects underscore the importance of taking into
314 account regulations and medical practice regarding late terminations when
315 comparing stillbirth and neonatal mortality rates between countries.

316

317 **Conclusion**

318 Terminations of pregnancy between 22 and 31 weeks GA represent a high proportion
319 of singleton very preterm births and stillbirths in France. The inclusion of all
320 terminations in studies, not only those for congenital anomalies, is needed to
321 understand medical practices, variations in preterm birth and stillbirth rates as well as
322 infant health indicators in the perinatal period.

323

324 **Acknowledgements**

325 We thank the members of the EPIPAGE 2 Study Group and all the regional teams for
326 their participation in the study and for their contribution to data acquisition. We
327 acknowledge the collaborators of the EPIPAGE 2 Obstetric Writing Group including
328 the following: Pierre-Yves Ancel, MD, PhD (Inserm UMR 1153, Obstetrical, Perinatal
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420

421 All the collaborators of the EPIPAGE 2 Obstetric writing group have no conflict of
422 interest or compensation in relation with this article to disclose. All of them consented
423 to such acknowledgment.

424

425 **Disclosure of interests**

426 The authors report no conflict of interest

427

428 **Authorship**

429 IM, JZ and BB analysed the data and drafted the manuscript. NL, AB, BK and PYA
430 participated in the interpretation of the results and made suggestions for revisions.

431 PYA contributed to the design of the study.

432

433 **Details of ethics approval**

434 Ethics approval was received from the National Data Protection Authority (CNIL no.
435 911009) and Consultative Committee on the Treatment of Information on Personal
436 Health for Research Purposes (approval granted 18 November 2010; reference
437 number 10.626) and Committee for the Protection of People Participating in
438 Biomedical Research (approval granted 18 March 2011, reference CPP SC-2873).

439

440 **Funding**

441 The EPIPAGE 2 study was funded and supported by: (1) the French Institute of
442 Public Health Research/Institute of Public Health and its partners: the French Health
443 Ministry, the National Institute of Health and Medical Research (INSERM), the
444 National Institute of Cancer, and the National Solidarity Fund for Autonomy (CNSA);
445 (2) the French EQUIPEX programme of investments in the future; and (3) the
446 PREMUP Foundation.

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