Feticide in second- and third-trimester termination of pregnancy for fetal anomalies: Results of a national survey

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What's already known about this topic?

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

What does this study add?

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

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

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

Abstract

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

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

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

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

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

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

Introduction

The growth of prenatal diagnosis over the last 3 decades has greatly increased the rate of prenatal detection of fetal anomalies. This rate varies among European countries, but ranges between 30 and 80% according to data from the European registers[1-3]. Certain fetal anomalies can lead to the organization of specific perinatal management, sometimes with the possibility of specific fetal therapy[4,5]. In most European countries, termination of pregnancy for fetal anomalies (TOPFA) may be requested by the parents when the anomalies are severe, considered incurable, and associated with a high risk of severe disability. However, the legislative provisions, notably concerning a time limit beyond which TOPFA is no longer authorized, vary from one country to another.

French law authorizes TOPFA when there is a strong probability that the **fetus** has a particularly serious anomaly recognized as incurable at the time of diagnosis[6]. In France, there is no gestational age cut-off. When a **pregnant woman** opts for TOPFA, two fetal medicine specialists who are members of a prenatal diagnosis (PD) center must attest that the fetal anomaly is covered by the legal provisions in force.

Although the World Health Organization recommends feticide for elective termination of pregnancy after 20 weeks, in France, as in most other European countries, there is no legal obligation to perform this procedure in the framework of TOPFA. Several studies have examined the technical aspects of feticide, notably concerning the lethal substances used and their route of administration, ie, fetal or intra-amniotic injection[7-11]. Some studies have examined the psychological experiences of both the parents and the healthcare professionals involved[12-14]. Expert opinions have also been formulated concerning the ethical issues associated with whether or not feticide should be performed in the setting of TOP, whatever the

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

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

Material and methods

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

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

Results

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

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

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

Discussion

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

While the World Health Organization recommends feticide for late TOP, in France, unlike other countries, there is no legal obligation to perform feticide. Yet, feticide appears to be ethically justified when it prevents **neonatal demise associated with a risk of suffering or pain**[15-18]. Studies in the literature on late TOP concern in large part second-trimester TOP, and notably TOP performed according to the wishes of the parents, in the context of a normal pregnancy. These TOP are authorized in several countries up until 24 weeks, as in the UK. Given that almost all these TOP are performed using a surgical technique, the question of fetal survival does not arise. The context of TOP for fetal anomalies is different because TOP is legal after 22 weeks, notably in several European countries. In TOPFA, in most cases, it may be helpful to perform a postmortem examination of the fetus to define the fetal disease and to facilitate genetic counseling for subsequent pregnancies. It is against this backdrop of induction of labor that feticide is posed. However, there is the question of its acceptability to **pregnant women** and to healthcare professionals. Most studies of feticide have focused on its technical aspects: route of fetal injection, type of lethal substance used, and so forth[7-10]. These studies mainly concentrated on maternal risks. It was thus shown that injection in the umbilical vein involved the least risk to the **pregnant woman**[7]. It seems that xylocaine is associated with the lowest maternal risk and achieves fetal asystole in most cases[8]. Some authors consider that intracardiac injection is surer, and in some

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

Although little discussed in the literature, feticide requires experience of invasive, ultrasound-guided procedures. This may be a limiting factor in the organization of some teams. In our study, 19/39 centers reported that TOPFA requiring feticide was performed in the maternity unit of the PD center because other maternity units in the region had no physician able to perform the procedure. Interestingly, the intra-amniotic injection of digoxin in TOP has been reported to achieve fetal demise within about 24 hours[10]. This injection is technically simpler than injection in the umbilical cord or intracardiac injection. In a recent study, this technique achieved fetal demise in up to 93% of reported cases[10]. The risk of failure seemed to be greater in the case of maternal obesity. The results of this study are interesting as they could argue in favor of easier access to this procedure, notably for couples living far from tertiary centers. However, the precise time lapse between intra-amniotic injection and fetal death is unknown. Our study shows that most French CPNs perform fetal anesthesia before feticide in accordance with the guidelines of the French College of Obstetricians and Gynecologists[21]. Interestingly, fetal pain is little considered in studies on late TOP.

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

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

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

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

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

	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

Table 2: Site of injection of the fetal anesthesia and lethal substance among the 39 prenatal diagnosis centers

	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