



Original Article

# A view of maternal mortalities in women conceiving through assisted reproductive techniques: A nation-based study of Turkey

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## Abstract

**Background:** Our aim was to evaluate maternal mortality causes among Turkish women giving birth after assisted reproductive techniques (ARTs).

**Methods:** All maternal deaths following conception with ART pregnancies were identified through the National Maternal Mortality Surveillance System. We analyzed the system data collected between 2007 and 2014. During this period, there were 10,369,064 live births and 1788 maternal deaths resulting from both direct and indirect causes. We identified 28 maternal death cases following ART procedures. The age, gestational age at birth, number of antenatal visits, delivery route, time of death, cause of death, and neonatal outcomes were recorded. Also, any existing delay (phase 1, 2, or 3) and preventability of maternal death were assessed.

**Results:** Hypertensive disorders, pulmonary embolism, and cardiovascular disease were the leading causes of maternal death. Twelve (40%) women were over 35 years of age. Of the deaths, 15 (54%) were attributed to indirect causes. The number of unpreventable maternal deaths was 19 (67.9%), and 9 (36%) were classified as preventable after being assessed by the review commission of maternal mortality.

**Conclusion:** Pregnancies conceived with ARTs should undergo a careful assessment of risk factors for hypertensive disorders, pulmonary embolism and cardiovascular diseases. Those women require closer antenatal surveillance because 1/3 of these deaths were preventable.

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**Keywords:** Cause of death; Hypertensive disorders; In vitro fertilization; Maternal death; Perinatal outcome; Pulmonary embolism

## 1. Introduction

Maternal mortality is a socioeconomic and cultural indicator that reflects a country's general state of health care.<sup>1</sup> The United Nation's fifth Millennium Development Goals set targets for reducing maternal mortality by 2015.<sup>2</sup> The maternal mortality

ratio (MMR) of Turkey in the 2007–2009 period was 19.7 per 100,000 live births.<sup>3</sup> Many maternal deaths are preventable, and a review of the underlying clinical and social risk factors is important to decrease the number of these deaths.

Assisted reproduction techniques (ARTs) have become widely used in the treatment of human infertility. It is well known that pregnancies after ARTs have more complications than spontaneous pregnancies. With the increasing use of ARTs, the rates of both obstetrical complications, such as antenatal bleeding, multiple pregnancy, gestational hypertension, placenta previa, placental abruption, gestational diabetes mellitus, and prenatal complications (e.g., preterm delivery, low birth weight,

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and fetal growth restriction) increase.<sup>4,5</sup> Although poorly understood, these medical complications may have an effect on the ART process or may be related to associated medical problems and conditions, including the subfertility status.<sup>5</sup>

Herein, we aim to evaluate all Turkish maternal deaths in women conceiving through ARTs between January 2007 and December 2014.

## 2. Methods

This study was approved by the Zekai Tahir Burak Women Health and Research Hospital ethics committee, and the tenets of the Declaration of Helsinki were followed. After the approval, we retrospectively reviewed the national health ministry records of maternal deaths following ART pregnancies between January 2007 and December 2014. All maternal deaths following pregnancies with ARTs were identified through the National Maternal Mortality Surveillance System. We analyzed the system data encompassing an 8-year period.

In Turkey, all of the deaths are recorded to a government software program defined as the Death Notification System (DBS). The system does not allow burial without being recorded to the DBS. Maternal deaths in Turkey are identified by the pregnancy checkbox on the death certificate. The checkbox identifies whether the woman was pregnant at the time of death, within 42 days of death, within 43 days to 1 year of death, or not pregnant in the year before death. Thus, all maternal deaths per year were recorded accurately. All medical records pertinent to the maternal death (e.g., hospital, prenatal, and specialist) and any autopsy reports are requested and reviewed by a committee at the Turkish Health Ministry, including clinicians, 4 nurses, 1 perinatologist, 3 obstetricians, 1 internal specialist, and 1 anesthetist. The committee meets to conduct the reviews weekly. Parameters set out by the World Health Organization (WHO) in the ICD-10 regarding direct and indirect causes of maternal death were used.<sup>6</sup> Maternal death is defined as the death of a woman while pregnant or within 42 days of termination of the pregnancy, irrespective of the duration and site of the pregnancy and of any cause related to, or aggravated by, the pregnancy or its management, with the exception of accidental or incidental causes. Causes of maternal death were classified into 2 types: direct and indirect causes. Deaths resulting from obstetric complications, such as hypertension or postpartum hemorrhage, were defined as direct causes. Deaths resulting from a preexisting disease or a disease that developed during pregnancy and was not due to any of the direct obstetrical causes but was aggravated by the physiological effects of pregnancy, such as an infectious disease, neoplasm, or a circulatory system-related disease, were defined as indirect causes. The MMR was calculated as the number of maternal deaths during a given time period per 100,000 live births during the same time period.

During the study period, there were 10,369,064 live births and 1788 maternal deaths resulting from both direct and indirect causes. We identified 28 maternal death cases in women conceiving through ART procedures.

The age, gestational age at birth, number of antenatal visits, delivery route, time of death, and cause of death were recorded. Also, any existing delay (phase 1, 2, or 3) and preventability of maternal death were assessed. Phase 1 delay was defined as whether the patient decided to seek care; phase 2 delay was defined as the arrival at a health facility; and phase 3 delay was defined as the provision of adequate care in the clinic. Also, phase 0 was defined as unpreventable maternal deaths.<sup>7</sup>

Information on the forms was entered into an Excel spreadsheet. Data were then transferred into a statistical package.

## 3. Results

Table 1 presents the MMR of Turkey between 2007 and 2014. The mean MMR was calculated as 17.2 per 100,000 live births in this period. The MMR of Turkey resulting from the Maternal Mortality Registration System of the Ministry of Health in 2014 was 15.2 in 100,000 live births. There was a significant reduction in the country's MMR.

A total of 28 maternal deaths following ART pregnancies are summarized in Table 2. There were 476,000 ART cycles conducted in Turkey during the 8-year study period. The live birth rate among the ART cycles was 28.5% in the same period. Therefore, we determined that total live birth count as 135,660 after ART treatment, and the maternal death rate among ART cases was calculated as 20.6 per 100,000 live births. No significant difference was observed between the ART pregnancies and overall pregnancies in terms of MMRs (20.3/100,000 vs. 17.2/100,000,  $p > 0.05$ ). The mean  $\pm$  SD age was  $32.9 \pm 5.4$  years, and the median (minimum–maximum) duration of gestation at the time of maternal death was 31 weeks (7–38 weeks). Regarding the causes of maternal death following ART pregnancies, hypertensive disorders and cardiovascular disease were the 2 leading causes of maternal deaths (Table 3). Approximately 54% of maternal deaths following ARTs were attributed to indirect causes (e.g., pulmonary embolism, cardiovascular disease, fulminate hepatic failure, and intracranial hemorrhage).

Table 3 depicts the demographic and clinical characteristics of cases. Twelve women (40%) were aged  $>35$  years. Nine women (32%) were pregnant with twins. Of the women, 24 women (88%) had 4 or more antenatal visits, and 19 women (68%) had a cesarean delivery. Two (7%) had perimortem

Table 1  
Maternal mortality ratio of Turkey.

Year	MMR in 100,000 livebirths	Annual rate decline (%)
2007	21.2	8,49
2008	19.4	5,15
2009	18.4	10,87
2010	16.4	5,49
2011	15.5	0,65
2012	15.4	3,25
2013	15.9	4,40
2014	15.2	9,87

Table 2  
Causes of maternal death in women conceived by in vitro fertilization.

Causes Of Death	n (%)
Direct causes	
Hypertensive disorders	8 (28)
Chorioamnionitis	3 (11)
Uterine atony	2 (7)
Indirect causes	
Cardiovascular disease	5 (19)
Pulmonary embolus	4 (13)
Intracranial hemorrhage	1 (4)
Fulminant hepatic failure	2 (7)
Others	3 (11)

cesarean sections, and 22 women (78%) were lost during puerperium (see Table 4).

The number of unpreventable maternal deaths was 19 (68%). Among maternal deaths, 9 (36%) were classified as preventable. Two deaths (7%) were due to the patients' lack of knowledge and attitude (phase 1 delay). Providing and receiving timely care after reaching the referral site was a problem among 7 (25%) women (phase 3 delay). Phase 3 delay was seen in 1 (3%) patient due to inappropriate management of severe preeclampsia (see Fig. 1).

#### 4. Discussion

Maternal death is an important worldwide health problem, especially for developing countries. Because the averseness to high-risk pregnancies has increased, complications and delays

in the management of these complications threaten mothers' lives. Furthermore, due to the widespread use of ARTs, obstetric and neonatal morbidities have risen. In this descriptive retrospective study, we aimed to evaluate the demographic characteristics of maternal death of those conceiving through ARTs. During the study period, 28 maternal deaths were conceived through ARTs among 1788 maternal deaths. The mean age of the cases was  $33.2 \pm 5.6$ , and the median gestational age at death was 31 weeks of gestation. There were 13 direct causes and 15 indirect causes of death, and the most common cause of death was cardiovascular disease.

The prevalence of hypertensive disorders is increasing in ART pregnancies. Say et al. combined 417 data points from 115 countries and studied 62,378 maternal deaths.<sup>2</sup> They reported a 14% ratio of maternal deaths caused by hypertensive disorders. Shevell et al.<sup>8</sup> found a 2.7-fold increase in the incidence of preeclampsia in 554 ART pregnancies. Allen and Wilson<sup>9</sup> reported a 2-fold increase in hypertensive disorders in women with ART pregnancies compared with spontaneous conceptions. In Turkey, in a 7-year period, there were 8 maternal deaths due to hypertensive disorders of pregnancy in women conceiving through ARTs. In 1 patient, phase 3 delay was seen due to inappropriate management of severe preeclampsia. We found the rate of maternal deaths caused by hypertension to be 28%. Among these deaths, 3 were caused by HELLP syndrome. Women conceiving through ARTs require closer antenatal surveillance for hypertensive disorders of pregnancy. The increase in the maternal mortality rate due to hypertensive disorders following ARTs was caused by the

Table 3  
Maternal death in ART pregnancies in the Turkey, 2007–2014.

Cases	Age (years)	Gestational week at death	Death time	Death cause	Delay phase	Pregnancy outcome
1	35	31	Post-partum first week	Diabetes Mellitus	0	Live birth
2	32	23	Post-partum first week	Chorioamnionitis	3	Abortion
3	34	35	Post-partum first week	Hypertensive disorders	0	Live birth
4	31	36	A week period after birth	Hypertensive disorders	1	Live birth
5	34	36	Post-partum first week	Acute fatty liver	0	Live birth
6	35	8	Pre-partum	Pulmonary embolus	0	Abortion
7	29	32	Post-partum first week	Cardiovascular diseases	0	stillbirth
8	36	19	Post-partum first week	Chorioamnionitis	3	abortion
9	30	30	A week period after birth	Cardiovascular diseases	0	stillbirth
10	29	30	Pre-partum	Pulmonary embolus	0	Live birth
11	24	28	Post-partum first week	Hypertensive disorders	3	Live birth
12	24	30	Post-partum first week	Intracranial hemorrhage	0	Live birth
13	27	32	A week period after birth	Pulmonary embolus	0	Live birth
14	36	35	Post-partum first week	Hepato-renal syndrome	0	stillbirth
15	41	32	Post-partum first week	Hypertensive disorders	0	Live birth
16	36	37	Post-partum first week	uterine atony	3	stillbirth
17	30	15	Pre-partum	Cardiovascular diseases	0	stillbirth
18	25	32	Post-partum first week	Hypertensive disorders	0	Live birth
19	33	34	Post-partum first week	DIC (lympho-proliferative disease)	0	Live birth
20	40	38	A week period after birth	Sepsis	0	Live birth
21	39	29	A week period after birth	Hypertensive disorders	0	Live birth
22	42	28	Post-partum first week	Cardiovascular diseases	3	Live birth
23	40	10	Pre-partum	Intra-abdominal arterio-venous malformation	0	stillbirth
24	27	30	A week period after birth	Hypertensive disorders	0	Live birth
25	36	7	Pre-partum	Pulmonary embolus	3	stillbirth
26	34	38	A week period after birth	Cardiovascular diseases	3	Live birth
27	24	26	Post-partum first week	Uterine atony	1	Live birth
28	39	18	Post-partum first week	Chorioamnionitis	0	abortion

Table 4  
Demographic and clinical characteristics of cases.

	n	%
Age (years)		
<25	4	14
25–35	12	46
>35	12	40
Birth weight (g)		
<1500 g.	7	32
1500–2500	10	45
>2500	5	23
Gestational age at birth		
1.trimester	4	14
2.trimester	5	18
3.trimester	19	68
Preterm labor	6	21
Hypertensive disorders	7	25
Gestational Diabetes Mellitus	1	3,5
Systemic disorders	7	25
Twin pregnancy		
yes	9	32
no	19	68
NICU requirement		
yes	11	72
no	6	28
Pregnancy outcome		
Abortion	4	15
Stillbirth	7	25
Live birth	17	60
APGAR 5th minute		
≤7	7	43
>7	10	57
Final outcome of pregnancy		
caesarean	19	68
vaginal	3	11
abortion	4	14
Unrealized labor	2	7
Death timing		
Pre-partum	6	22
Early post- partum	15	53
Late post-partum	7	25
Delay phase		
0	19	75
1	2	4
2	–	–
3	7	21

NICU: Neonatal intensive care unit.

increase in hypertensive disorders in ART pregnancies. We recommend that all maternity units should have clear guidelines for the management of severe preeclampsia and that treatment protocols should include intravenous antihypertensive agents. The examination of hypertensive diseases in all ART pregnancies has been a limitation of our study.

Braat et al.<sup>10</sup> evaluated all deaths following ARTs in the Netherlands in a 24-year period and found that the major causes of death directly related to ARTs were sepsis and ovarian hyperstimulation syndrome. In a study by Venn et al.,<sup>11</sup> the overall mortality rate in ART patients in Australia was significantly less than that in the general female population. Regarding the causes of maternal death, pulmonary embolus and cardiovascular disease were the 2 leading causes of maternal death, followed by hypertensive disorders, in Turkey in the study period. During

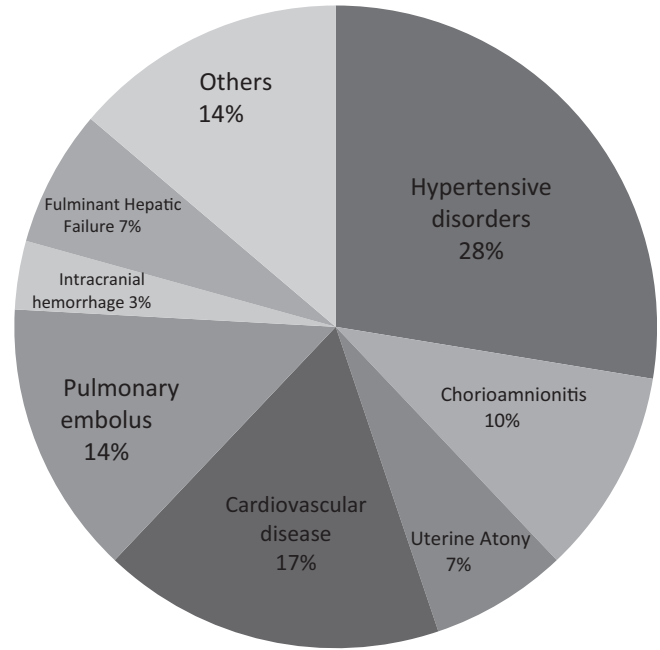


Fig. 1. The cause of maternal death by autopsy in Turkey from 2007 to 2014 in patients conceived with ART.

the study period, 2 deaths were caused by septic abortion. These cases were twin pregnancies that ended in deaths after abortion of the first fetuses at the second trimester. In twin pregnancies, follow-up of the second fetuses after abortion of the first fetuses increased the maternal morbidity and mortality. Roman et al. reported on 19 delayed-interval deliveries and concluded that the procedure is associated with a significant risk of serious maternal morbidity.<sup>12</sup> It is known that multiple pregnancy rate and abortion rate increases with ART pregnancies. When an abortion occurs with a twin ART pregnancy, the expectation and fear of the other baby's survival increases, and this puts pressure on physicians. Thus, a “healthy decision-making ability” is weakened. In both cases, phase 3 delay occurred and sepsis-induced disseminated intravascular coagulation was the major cause of death. Patients with delayed-interval delivery should be counseled and followed up carefully regarding the risks and benefits of the procedure, including the >30% risk of major maternal morbidity ranging from hemorrhage to septic shock.

Recently, Hansen et al.<sup>13</sup> carried out a national register-based cohort study to find the risk of venous thrombosis in pregnancies after ARTs and revealed a significantly increased venous thromboembolism (VTE) risk throughout pregnancy and the post-partum period in ART pregnancies. An excess VTE risk was found to be most prominent during the first trimester and the first 6 weeks postpartum. In another study, the incidence of first-trimester VTE in relation to ARTs was found to be 0.2%, representing a 10-fold increase compared with the background population.<sup>14</sup> Pulmonary embolism occurred in 4 cases who conceived through ARTs in Turkey. Failure of consideration for thromboprophylaxis with low molecular weight heparin was noted in 2 patients. Royal College advises that women with an ART pregnancy and 3 other risk factors should be considered for

thromboprophylaxis with low molecular weight heparin starting in the first trimester.<sup>15</sup>

Shevell et al.<sup>8</sup> found a 2.7-fold increase in the incidence of preeclampsia in this group of women. Allen and Wilson<sup>9</sup> published a review and revealed a 2-fold increase in hypertensive disorders of pregnancy in women with ART pregnancies compared with spontaneous conceptions. In Turkey, in an 8-year period, there were 7 maternal deaths due to hypertensive disorders of pregnancy in women conceiving through ARTs. Phase 3 delay was seen in 1 patient due to inappropriate management of severe preeclampsia. Women conceiving through ARTs require closer antenatal surveillance for hypertensive disorders of pregnancy.

In conclusion, because of increased risk factors, women conceiving through ARTs should undergo a careful assessment of risk factors for pulmonary embolism and cardiovascular diseases and require closer antenatal surveillance for hypertensive disorders of pregnancy.

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