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The importance of perinatal autopsy. Review of the literature and series of cases

MARIA ŞOROP-FLOREA[1)], RALUCA NICULINA CIUREA[2)], MIHAI IOANA[3)], ALEX EMILIAN STEPAN[2)], GEORGE ALIN STOICA[4)], FLORENTINA TĂNASE[1)], MARIA CRISTINA COMĂNESCU[1)], MARIUS-BOGDAN NOVAC[5)], IOANA DRĂGAN[6)], CIPRIAN LAURENŢIU PĂTRU[1)], ROXANA CRISTINA DRĂGUŞIN[1)], GEORGE LUCIAN ZORILĂ[1)], OVIDIU MARIAN CĂRBUNARU[1)], NUŢI DANIELA OPRESCU[6)], IULIANA CEAUŞU[6)], SIMONA VLĂDĂREANU[7)], ŞTEFANIA TUDORACHE[1)], DOMINIC GABRIEL ILIESCU[1)]

[1)]*Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania*

[2)]*Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania*

[3)]*Human Genomics Laboratory, University of Medicine and Pharmacy of Craiova, Romania; Emergency County Hospital, Craiova, Romania*

[4)]*Department of Pediatric Surgery, University of Medicine and Pharmacy of Craiova, Romania; Emergency County Hospital, Craiova, Romania*

[5)]*Department of Anesthesiology and Intensive Care, University of Medicine and Pharmacy of Craiova, Romania; Emergency County Hospital, Craiova, Romania*

[6)]*Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[7)]*Department of Obstetrics–Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

Abstract

Perinatal autopsy remains the gold-standard procedure used to establish the fetal, neonatal or infant abnormalities. Progressively, perinatal pathology has become a specialized field with important roles of audit for fetal prenatal diagnostic tools, in parents counseling regarding future pregnancies, in scientific research, for epidemiology of congenital abnormalities and teaching. The differences between prenatal ultrasound and autopsy reports represent a strong argument for the autopsy examination following termination of pregnancy. The reasons for such discrepancies are related to the ultrasonographic or pathological examination conditions, the type of the anomalies, the expertise and availability of the operators. Several facts led to an undesirable increase of refusals from parents to consent to a conventional invasive autopsy: the centralization of pathology services, the poor counseling provided by non-experts in fetal medicine and the clinicians' over-appreciation of the importance of the ultrasound diagnostic investigation. Although non-invasive alternatives have been tested with promising results, conventional autopsy remains the gold standard technique for the prenatal diagnosis audit. We report and analyze several cases of prenatally diagnosed malformed fetuses with different particularities that underline the necessity of perinatal autopsy. We discuss the antenatal findings and management and post-mortem autopsies in the respective pregnancies.

Keywords: perinatal autopsy, congenital malformations, ultrasound, prenatal diagnosis.

Introduction

The general use and the accuracy of prenatal ultrasound screening for fetal abnormalities has rapidly improved, due to the technological development of ultrasound machines combined with increasing training in prenatal diagnostic for obstetricians and sonographers, in the last decades [1]. Perinatal autopsy remains the gold-standard procedure used to confirm the abnormalities in terminated or aborted fetuses, and deceased neonates or infants. Consequently, this investigation plays an important role in the quality control of the imagistic evaluations.

Since the early development of anomaly scan, numerous good quality studies have compared the fetal and neonatal suspected anomalies at the fetal ultrasound scan with autopsy findings. We therefore performed a review of literature regarding the correlation between prenatal/ perinatal findings and fetal or neonatal autopsy in order to provide valuable information for the parents counseling carrying malformed fetuses. Several cases from our practice are presented to express the advantages of the perinatal autopsy.

Methods

We conducted a search in PubMed, Medline, Embase and Cochrane library databases up to April 2017 to find and analyze the communications that evaluated the agreement between fetal or neonatal autopsy and perinatal diagnosis of fetal anomalies. The key words were: ultrasound, pathology, prenatal diagnosis, fetal anomaly, malformation, termination of pregnancy, stillbirth, fetal autopsy. Sixty-four papers were analyzed [2–65], and we found that it is hard to link together the results of all these studies, because their inclusion criteria are heterogeneous. The design of the researches included variably neonatal deaths, therapeutic terminations and fetuses with intrauterine demise or chromosomal abnormalities.

The autopsy rate, the level of the unit involved, the expertise of pathologists and the autopsy protocol differ widely. The population risk is often not mentioned (*e.g.*, whether patients were inborn or referred); also, the antenatal diagnosis, the gestational age at ultrasound examination and pregnancy termination is frequently missing. Although most of the researches report the investigation of the entire fetus, some studies refer exclusively to a certain fetal system, *e.g.*, cardiovascular, central nervous or urinary. Another important limitation of the available literature is related to the proper investigation of the anomaly scan accuracy: almost all of the studies are retrospective; the autopsy rate in the terminated pregnancies or stillbirths is usually reported less than the rate of 75% – as recommended in specialty guidelines; and most of the papers have exclusively included termination of pregnancy (TOP) due to prenatally ultrasound detected anomalies, but the authors did not commented the follow-up of the rest of the fetuses and the false negative results (missed abnormalities) of the anomaly scan.

Results

The role of perinatal autopsy

Progressively, perinatal pathology demanded increasing expertise and has become a specialized field of general pathology. Besides the **audit** role for fetal diagnosis and therapeutic techniques [20–25, 32–35, 41], we should also consider the role of autopsy for **teaching** and **research** purposes [32, 41]. However, the most important role of perinatal autopsy is to confirm and complete the **diagnosis** of fetal malformations, including findings not seen prenatally and to refine the initial diagnosis that may require histological, genetic or X-ray evaluation and storage of tissue samples for future microscopic, genetic and biochemical analysis, if these studies have not been performed prenatally [34]. Through all these components, fetal autopsy is of great importance in **counseling** the parents regarding the risk of recurrence and in targeting tests in future pregnancies.

Regarding the diagnostic role of perinatal autopsy, an important body of literature reveals the value of perinatal autopsy (Table 1).

Table 1 – ***The performance of perinatal autopsy to confirm or add information of clinical importance***

Study, year, reference	No. of autopsies: fetal / neonatal	Percentage of cases with new information of clinical importance added by autopsy
Rutledge *et al.*, 1986 [2]	45 neonates	76% – additional findings not detected by PUs.
Meier *et al.*, 1986 [3]	52 fetuses 87 neonates	26% – (17.3% fetal cases and 31.03% of the neonatal cases) established the cause of death; 48% – highlighted the need for specific genetic counseling or evaluation.
Benacerraf *et al.*, 1987 [4]	49 fetuses with CHD	43% of the CHD – not detected with PUs.
Manchester *et al.*, 1988 [5]	212 fetuses	37% – additional findings not detected by PUs.
Crawford *et al.*, 1988 [6]	74 fetuses with CHD	20% of the CHD – not detected with PUs.
Johns *et al.*, 2004 [7]	47 fetuses	46.8% – complete agreement with PUs; 23.4% – minor additional findings not detected by PUs (major agreement); 27.7% – significant additional findings not detected by PUs; 12.8% – established the definitive diagnosis; 2.1% – complete discordance with PUs.
Shen-Schwarz *et al.*, 1989 [8]	61 fetuses	46% – significant additional findings not detected by PUs; 49% – complete or major agreement with PUs; 5% – less information than PUs due to tissue autolysis.
Allan *et al.*, 1989 [9]	41 fetuses with CHD	17.07% – significant additional findings not detected by PUs.
Clayton-Smith *et al.*, 1990 [10]	133 fetuses 2nd trimester TOP	39.85% – significant additional findings not detected by PUs; the risk of recurrence (genetic counseling) was revised.
Weston *et al.*, 1993 [13]	153 fetuses	44% – significant additional findings or disagreement with PUs; 25% – the risk of recurrence (genetic counseling) was revised.
Grant *et al.*, 1993 [14]	175 fetuses	21.14% – significant additional findings not detected by PUs; 1.71% – complete disagreement with PUs; 10.86% – major agreement (diagnosis confirmed, with additional features of academic interest only); 9.14% – prenatal transient abnormal features, normal baby at birth.
Julian-Reynier *et al.*, 1994 [15]	158 fetuses 2nd trimester TOP	90% – complete agreement with PUs; 3% – complete disagreement with PUs; 7% – the US predicted anomaly was absent; 57% of the multiple malformed cases – the prenatal US missed at least one diagnosable anomaly; 13% of the single malformed cases and in 53% of the multiple ones, (30% of all the cases) – the risk of recurrence (genetic counseling) was revised.
Chescheir & Reitnauer, 1994 [16]	133 fetuses and neonates	13% of autopsy demonstrated major abnormalities were missed by PUs; 39% of all malformations detected were missed by PUs.
Medeira *et al.*, 1994 [17]	215 fetuses 2nd trimester TOP	42.3% – discordance with PUs (diagnostic modified or refined); 1.39% – discordance with PUs (abnormality suspected by PUs not confirmed).
Allan *et al.*, 1994 [18]	886 fetuses with CHD	7.67% – partial agreement with PUs (main diagnosis confirmed but additions to the central diagnosis); 10.83% – major discordance with PUs (main diagnosis incorrect).

Study, year, reference	No. of autopsies: fetal / neonatal	Percentage of cases with new information of clinical importance added by autopsy
Ramalho *et al.*, 2006 [19]	76 fetuses	61.1% – complete agreement with PUs; 27% – major agreement with additional information; 11.84% – risk of recurrence of the anomaly was revised; 0% – absolute discordance.
Cartlidge *et al.*, 1995 [20]	168 fetuses 64 neonates	26% – significant additional findings not detected by PUs; 18% – disclosed the cause of death.
Saller *et al.*, 1995 [21]	94 perinatal deaths ≥20 GW and ≤48 hours after birth	44.7% – disagreement with PUs (changed or significantly data added to the diagnosis).
Isaksen *et al.*, 1998 [22]	140 fetuses with CNS anomalies	89% – complete agreement with PUs; 5% – major agreement with PUs (minor additional findings); 6% – disagreement with PUs (changed or significantly data added to the diagnosis).
Tennstedt *et al.*, 1998 [23]	183 fetuses (14–24 GW) 2nd trimester TOP	78% – major agreement with PUs; 20% – significant additional findings not detected by PUs; 2% – major disagreement with PUs (malformations not confirmed).
Sun *et al.*, 1999 [24]	61 intact fetuses following TOP	65.6% of CNS cases and 47.5% of other systems – complete agreement; 6.5% of CNS cases and 27.9% in other systems – major disagreement; ▪ better correlation for renal anomalies (complete agreement in 63.6%, two FP and no FN) than CHD (complete agreement in 27.3%, five FP and three FN).
	36 fragmented fetuses from dilatation and surgical evacuation	▪ US diagnosis in the CNS could not be confirmed totally (69.4%) or partially (2.8%) due to fragmentation; ▪ US diagnosis of other systems was confirmed in 16.6%.
Faye-Petersen *et al.*, 1999 [25]	128 fetuses 11 neonates – 97 without malformations; – 41 with malformations.	51% – additional abnormalities found in cases with malformations; 10% – additional pathology that altered counseling in cases without malformations; 27% – revealed the unsuspected cause of neonatal death; 26% – counseling and recurrence risk estimates altered overall.
Isaksen *et al.*, 1999 [26]	101 fetuses with CHD	73.3% – complete agreement with PUs; 17.8% – major agreement with PUs (minor additional findings); 9% – significant additional findings not detected by PUs.
Isaksen *et al.*, 2000 [27]	112 fetuses with urinary system abnormalities	86.61% – complete agreement with PUs; 4.5% – major agreement with PUs (minor additional findings); 1.78% – major agreement with PUs (minor PUs findings not confirmed); 7.14% – significant additional findings not detected by PUs.
Laussel-Riera *et al.*, 2000 [28]	300 fetuses 2nd trimester TOP	41% – significant additional findings not detected by PUs; 20.3% – major disagreement (changed the prenatal “hypothesis”); 38.7% – major agreement (confirmed the diagnosis hypothesis).
Carroll *et al.*, 2000 [29]	61 fetuses with brain abnormalities other than neural tube defects	77% – major agreement with PUs; 43% – agreement in cases prenatally diagnosed with Dandy–Walker malformation or variant.
Brodlie *et al.*, 2002 [31]	209 neonates	74% – complete agreement with PUs; 23% – additional findings not detected by PUs; 3% – significant additional findings not detected by PUs, crucial for future counseling.
Yeo *et al.*, 2002 [32]	88 fetuses with malformations	65% – complete or major agreement; ▪ PUs sensitivity ≥70% in central nervous system, cardiac system, urinary system, extremities, genitalia, ribs, and hydrops; ▪ PUs sensitivity for fetuses with anomalies – 97%; ▪ PUs detection rate 75% for major and 18% for minor abnormalities from 299 major and 73 minor abnormalities found on autopsy.
Kock *et al.*, 2003 [33]	273 fetal deaths	9% – major disagreement with PUs (autopsy changed the diagnosis); 22% – additional information was obtained.
	351 neonatal deaths	10% – major disagreement with PUs (autopsy changed the diagnosis); 40% – additional information was obtained.
Boyd *et al.*, 2004 [34]	132 fetuses TOP with normal karyotype	71.97% – complete or major agreement with PUs; 26.51% – significant additional findings not detected by PUs, important for counseling.
Sankar *et al.*, 2006 [35]	206 fetuses: – 138 TOP abnormal; – 68 spontaneous losses.	1.45% – disagreement (PUs abnormalities not confirmed); 37.38% – additional information was obtained not detected by PUs; 11.65% – significant additional information crucial for future counseling changed of recurrence risk.
Kaasen *et al.*, 2006 [36]	274 fetuses 2nd trimester TOP	58.4% – complete agreement with PUs; 31.4% – additional findings (in addition to those leading to termination) not observed by PUs; 9.9% – disagreement with PUs observations (in addition to those leading to termination) – not confirmed.
Papp *et al.*, 2007 [37]	305 fetuses 2nd trimester TOP for trisomies (21, 18, 13)	35.8% – complete agreement with PUs; 64.2% – additional findings (involving mainly two organ systems: face and extremities); 16.06% – disagreement with PUs findings (abnormalities not confirmed).

Study, year, reference	No. of autopsies: fetal / neonatal	Percentage of cases with new information of clinical importance added by autopsy
Akgun *et al.*, 2007 [38]	107 fetuses 2nd trimester TOP	100% – major agreement regarding major anomalies leading to TOP; 77% – overall detection rate in prenatal US for major and minor anomalies; 20% – additional minor anomalies not detected at PUs; 3% – disagreement regarding minor anomalies (not confirmed during autopsy).
Amini *et al.*, 2006 [39]	328 fetuses	91.2% – complete or major agreement with PUs; 7% – PUs findings not confirmed, but postnatal findings of similar severity; 1.8% – the anomaly proved to be less severe than was predicted PUs; 47% – significant additional findings not detected by PUs; 10% – significant additional findings - a syndrome was disclosed.
Antonsson *et al.*, 2008 [40]	112 fetuses 2nd trimester TOP	45% – complete agreement with PUs; 40% – significant additional information of clinical importance; 11% – partial disagreement; 4% – complete disagreement; ▪ areas of discrepancy involved mainly CNS and cardiovascular abnormalities; ▪ 62% agreement rate in CNS abnormalities: highest in acrania/ anencephaly (92%) and lowest in hydrocephaly (39%).
Phadke *et al.*, 2010 [41]	91 fetuses TOP	67.03% – major agreement with PUs; 32.97% – significant additional findings redefined diagnosis and recurrence risk.
Vogt *et al.*, 2012 [42]	455 fetuses and neonates with congenital anomalies at autopsy	84% – complete agreement with PUs; 14.72% – additional findings not influencing counseling; 0.88% – significant additional findings that influenced further counseling; 98% – agreement regarding the main diagnosis.
	408 fetuses and neonates from a previous 10-year period	75% – complete agreement with PUs; 90% – agreement regarding the main diagnosis.
Thornton & O'Hara, 1998 [43]	174 perinatal deaths: – 18 late fetal losses; – 70 stillbirths; – 57 neonatal deaths; – 29 post neonatal deaths.	43.1% – complete agreement; 13.22% – additional information which did not alter the cause of death or have implications for future pregnancies; 28.16% – significant additional findings that influenced further counseling; 15.52% – no positive information but excluded possible causes of death.
Porter & Keeling, 1987 [44]	150 fetal deaths	40% – complete agreement with PUs; 36% – significant additional information from autopsy with clinical importance; 26% – disagreement with the clinical diagnosis.
	150 neonatal deaths	19% – complete agreement with PUs; 66% – additional information provided by the autopsy; 15% – disagreement with PUs; 44% of neonatal deaths – new information with clinical importance; 20% – disclosed the cause of death.
Rajashekar *et al.*, 1996 [45]	261 perinatal deaths	37.7% – complete agreement with PUs; 59.5% – additional findings not detected by PUs; 19% – disagreement with PUs; 2.8% – no cause of fetal loss determined of fetal loss determined.
Pahi *et al.*, 1998 [46]	61 TOP for fetal anomaly	14.6% – complete agreement with PUs; 51% – additional findings not detected by PUs; 34.4% – disagreement with PUs.
Kaiser *et al.*, 2000 [47]	173 fetuses 2nd trimester TOP	49% – complete agreement with PUs; 51% – additional findings not detected by PUs; 4% – disagreement with PUs; 3% – no cause of fetal loss determined.
Dickinson *et al.*, 2007 [48]	809 TOP for fetal anomalies (>14 GW)	63.5% – complete agreement with PUs (in euploid cases); 15.1% – additional findings not detected by PUs; 1.1% – disagreement with PUs (autopsy added major diagnostic information).
Maessen & van der Matten, 2011 [49]	161 all fetuses	59% – complete agreement with PUs; 40% – additional findings not detected by PUs.
Hauerberg *et al.*, 2012 [50]	52 fetuses 2nd trimester TOP	46.1% – complete agreement with PUs; 44.2% – additional findings not detected by PUs.
Vimercati *et al.*, 2012 [51]	144 fetuses 2nd trimester TOP	49% – full agreement between US and autopsy; 34% – autopsy confirmed all US findings but revealed additional anomalies; 4% – total disagreement.
Rodriguez *et al.*, 2014 [52]	151 TOP for fetal anomalies <24 GA	86% – complete agreement with PUs; in 92.7% of cases, the main US findings were confirmed; 4.6% – additional findings not detected by PUs; 1.9% – autopsy didn't confirm all US findings; 7.2% – disagreement with PUs; 5.29% – autopsy added relevant information to the diagnosis and counseling.

Study, year, reference	No. of autopsies: fetal / neonatal	Percentage of cases with new information of clinical importance added by autopsy
Faugstad *et al.*, 2014 [53]	70 fetuses with omphalocele, 58 TOP, nine died *in utero*, three live born	66% – full agreement between US and autopsy findings; 26% – minor autopsy findings not detected at US; 6% – major autopsy findings not detected at US; 0% – none of the autopsy findings suspected at US; 3% – US findings not confirmed at autopsy.
Szigeti *et al.*, 2007 [54]	172 fetuses with trisomy 21	▪ high agreement (>60%) between sonographic and autopsy findings of all abnormalities of central nervous system (65.4%), heart (67.4%), fetal hydrops (100%), and cystic hygroma (93.3%); ▪ lower agreement between sonographic and autopsy findings of all abnormalities of abdominal abnormalities (46.2%), renal anomalies (50%), facial abnormalities (1.2%), and extremities (4.4%); ▪ 34.2% additional major findings at autopsy involving mainly heart, head, and abdominal anomalies.
Parkar *et al.*, 2009 [55]	151 TOP for fetal abnormality >12 GA autopsied	99% – agreement between US and autopsy findings (correct diagnosis of the major abnormality); 30.2% – additional findings on autopsy (additional autopsy findings were demonstrated in fifth of the 151 fetuses, of which limb abnormalities such as a missing digit or contractures were the most common); 0.7% – (only one case) were no pathological findings seen on post-mortem examination.
Haak *et al.*, 2002 [56]	13 TOP fetuses with cardiac anomalies	53.85% (7/13) – agreement between US and autopsy findings; 46.15% (6/13) – additional findings not detected by PUs.
Picone *et al.*, 2008 [57]	138 fetuses TOP, two centre	61% – agreement between US and autopsy findings; 29% – additional findings not detected by PUs (possible bias due to different operators in the two centers).
Lomax *et al.*, 2012 [58]	71 TOP for malformation	44% – full agreement between the ultrasound and autopsy findings; 46% – a near match between the ultrasound and autopsy findings; 10% – the ultrasound findings were only partially confirmed or not confirmed by autopsy; 1.41% (one case) – discrepancy between the ultrasound and autopsy.
Struksnæs *et al.*, 2016 [59]	1029 TOPs, included autopsy after neonatal death	88.1% – full agreement between ultrasound and autopsy findings; 97.8% – the main diagnosis was correct.
Kotecha *et al.*, 2014 [60]	59 fetuses terminated for limb anomalies	61% – complete concordance between antenatal and postnatal findings; 23.7% – additional major anomalies were observed, the commonest being orofacial clefts.
Godbole *et al.*, 2014 [61]	141 ST fetuses terminated for structural birth defects and/or severe (IUGR) or intra-uterine death	29.07% – complete agreement between ultrasound and autopsy findings; 46.09% – additional information that did not influence the final diagnosis and/or counseling was obtained by autopsy in 65/1416; 24.82% – additional information provided by autopsy that influenced the final diagnosis and/or counseling.
Nayak *et al.*, 2015 [62]	227 fetuses autopsied	23% – full agreement between US and autopsy; 37% – autopsy confirmed all US findings but revealed additional anomalies; 23% – disagreement between US and autopsy.

CHD: Congenital heart disease; TOP: Termination of pregnancy; PUs: Prenatal ultrasound; GW: Gestational weeks; CNS: Central nervous system; FP: False positive; FN: False negative; US: Ultrasound; GA: Gestational age; ST: Second trimester; IUGR: Intrauterine growth restriction.

In 10–76% of the cases, the investigation is reported to add ***new information of clinical importance*** that influence the genetic counseling, and the severity classification of the anomaly, establishes the diagnosis of a syndrome, changes the prenatal diagnosis or determine the etiopathological mechanism of the anomaly, as underlined before in a large meta-analysis [30]. Although the overall percentage in which the autopsy add significant information is reported between 20% to 25% of the studied TOPs, we observe a significant improvement of the agreement between the prenatal ultrasound scan and post-mortem pathological exam over the years, due to the evolution of prenatal diagnosis, in terms of equipment, knowledge and training.

A recent rigorous systematic review [66], that analyzed 3534 second trimester autopsied fetuses from 19 studies published in the last two decades, showed that approximately 22% of fetal anomalies are missed by ultrasound. What is important and highlights the progress of the sonographic prenatal diagnosis is that in only 2% to 3% of the cases, the respective additional autopsy findings led to a different fetal diagnosis and parental counseling for the future pregnancy.

An issue of great importance regarding the false ultrasound diagnoses may lead to unnecessary TOPs. The analysis of Rossi & Prefumo [66] shows that more than 80% of the additional pathological findings were minor anomalies and did not represent the main indication for TOP. However, this should not discourage the autopsy audit for the sonographic anomaly scan performance, because there is a 9% disagreement between prenatal diagnosis and autopsy almost equally divided in ultrasound findings unconfirmed at autopsy and pathology findings missed by ultrasound. In addition, when TOP is proposed, parents should be counseled with regard to the fetal anatomy scan limitations.

Factors influencing prenatal and postnatal diagnostic agreement

The differences between prenatal ultrasound and autopsy reports constitute a strong argument for the importance of autopsy evaluation following TOP. They refer to anomalies detected by the autopsy and not observed at the prenatal scan and the observations made prenatally during ultrasound evaluation and not confirmed by autopsy. There are many reasons for such discrepancies, related to the **examination conditions** or the **type of the anomalies**: the low gestational age – that implies small fetuses with structures difficult to evaluate; an abnormal amount of amniotic fluid (poly- or an-/oligo-hydramnios) – that greatly influences the proper visualization of the fetal structures; association of abnormal pregnancy genetics – with consequently more complex development anomalies. Noteworthy, the association of multiple anomalies was reported with the highest rate of discordance between the ultrasound scan and autopsy examination [66] and a potential explanation refers to an excessive attention of the examiner on certain severe or interesting abnormal aspects, leading to an overlooking of other coexisting abnormalities.

A significant time interval between fetal death and autopsy is associated with autolysis and decomposition that may alter severely the results of the autopsy [21, 22, 34, 67, 68]. Moreover, post-mortem changes of fetal anatomy may impair the proper post-mortem confirmation of certain malformations, as ventriculomegaly and posterior fossa anomalies [59]. Therefore, prenatal sonographic findings that were not confirmed by perinatal autopsy are not always due to sonographic errors.

Another important factor is that the prenatal detection of minor abnormalities is lower than that of major anomalies [32, 38]. Some minor malformations or abnormalities, especially of small structures are **not detectable** by the prenatal ultrasound scan at any time in pregnancy [34], and an important group of major malformations are not early detectable in pregnancy by sonography, as the respective organs have not yet fully developed structurally or functionally [69–73]. However, such conditions should be recognized at the fetal autopsy exam, as they may change the diagnosis and thus modify the prognostic from an isolated to a complex malformation or a syndrome with different future implications [3, 8, 10, 16, 17, 20–26, 28, 32–34, 74].

Another source of disagreement between prenatal fetal investigation and the subsequent autopsy is related to the **settings** in which the two investigations are taking place, regarding the technical possibilities and the abilities of the medical personnel, that provides the services. As the resolution of the ultrasound equipment has progressed in the last decades, the detection of fetal abnormalities has remarkably increased. A good example of this statement is provided by the study of Vogt *et al.* [42] that compared the results of two similar 10-year period autopsy studies, conducted in the period 1985–1994 and 1995–2004 in the same tertiary referral fetal medicine center, and analyzed in a similar manner. In the first 10-year period, there was a complete agreement in 75% of cases and the main diagnosis was correct in 90% of the cases. In the following decade, complete agreement between prenatal ultrasound and post-mortem autopsy reached 84% of cases, with 98% agreement regarding the main diagnosis. The significant differences indicate that the detection of fetal abnormalities has improved over time due to technological improvement of the diagnostic ultrasound equipment together with an increased expertise of sonographers [75, 76].

The importance of the skills and expertise of medical personnel that provides the prenatal anomaly scan is highlighted by the fact that the detection rate of fetal malformations at early or mid-trimester anomaly scan varies widely between centers, although similar equipment and examination protocol are used [71, 72, 77]. Regarding the importance of pathologist's expertise, the study of Thornton & O'Hara [43] showed that except for the Regional Centre, the quality of the perinatal infant autopsy did not reach the adequate standard in almost half (46.6%) of the autopsies performed.

An important aspect for sonographers practice is where prenatal diagnosis performs well and what are the fetal **structures or systems** whose defects are frequently missed. It appears that ultrasound evaluation for CNS, genito-urinary, skeleton and heart performs well and detects more than three quarters of the anomalies [66]. Similar rates are obtained when fetuses with proven chromosomopathy are scanned. This may be explained because of the special attention of the sonographers when the central nervous system (CNS) and heart are evaluated, knowing the high rate of fetal anomalies related to these systems. On the other hand, the skeleton dysplasias and genito-urinary major abnormalities are easy to detect. Also, the increased awareness regarding the potentially associated malformations to chromosomal defects is a strong argument for high detection rates in cases with abnormal karyotype. The thorax and digestive anomalies are associated with a moderate detection rate, of about two-thirds and limbs anomalies are in fact frequently missed, and less than one quarter are detected by ultrasound exam.

Decline or confidence in perinatal autopsy?

Even in this era of impressive progress in prenatal diagnosis, fetal autopsy should be routinely recommended in the management of the detected malformations, since it adds important information in about one quarter of the cases, or even revises the prenatal diagnosis in at least 5% of the cases. Still, there is an alarming decline of autopsy rate [30–34, 78–89], because of centralization of pathology services [78, 79], changes in clinicians' appreciation of the importance of the investigation [79–81] – mainly because of the improvements in diagnostic imaging, or because of the poor counseling provided by non-experts in fetal medicine or the non-implication of a pathologist in the counseling team [80, 82, 90–95]. These facts lead to refusals from parents to consent to a conventional invasive autopsy. To improve the quality of counseling provided by the professionals that activate

in fetal medicine, a series of measures have been proposed to increase their awareness regarding the importance of the perinatal autopsy. Some of them imply witnessing perinatal autopsies as part of the specialization, continuous education regarding the contribution of the post-mortem examination and the involvement of the perinatal pathologists in the training process [82]. A strong argument for the implementation of these training measures is the fact that almost twice as many parents who declined the autopsy later regretted their decision, compared with those who consent (34.4% *vs.* 17.4%) [82].

It is also worth mentioning that in the areas less affected by the decline of the autopsy rate has – for example in the Scandinavian Peninsula where autopsy rate is high up to 95%, it was noted a constant reduction in their stillbirth rates [79, 96, 97]. The perinatal autopsy is performed routinely in countries where the legislation states that any demise of unknown cause and/or taking place into a hospital unit must be investigated in order to explain the cause of death [96]. Cultural particularities play an important role in fetal autopsy uptake and are essential to identify culturally appropriate ways when approaching certain population groups for consent after fetal death [98].

Besides the parents' consent, there is another problem, regarding the specialized personnel limitations, even in highly developed regions. This may limit the autopsy rate and/or affects the value of the evaluation [20, 43, 99–101].

Current international guidelines recommend that an accurate post-mortem evaluation should be offered to all couples after termination of pregnancy or stillbirth and parents should be encouraged to accept this single most useful and informative investigation, which is the best thing to do in such cases [102–106]. As mentioned before, close co-operation between ultrasonographers and pathologists is mutually stimulating for the development of prenatal diagnosis and perinatal pathology [26].

In low-resources regions, the fetal pathological diagnosis is scarce not because a low uptake, but because its low availability, and correlated with a high incidence of major gynecological and obstetrical conditions, including abortion/stillbirth, undiagnosed fetal malformations or cancer [102, 103]. Delivering appropriate health care in countries is hampered. Thus, low-income vulnerable populations continue to be seriously affected by resource allocation issues. These are medical as well as ethical problems, as many of adverse outcomes are preventable in their future pregnancies.

Alternatives

The efforts to counteract the declining trend of perinatal autopsy rate were generally unsuccessful [83–86, 107]. For these reasons, magnetic resonance imaging, computerized tomography and tomographic angiography were proposed as alternatives for the invasive post-mortem examination [101, 103–115]. These high-resolution imaging techniques are more easily accepted by the parents because they are non-invasive, with an acceptable or good reliability and confidence of diagnosis when compared to conventional autopsy [108–111, 116, 117]. They also proved to have some advantages in cases of small fetuses or fetal brain autolysis and decomposition [110]. Comparing the diagnostic yield of whole-body post-mortem computed tomography imaging *versus* post-mortem magnetic resonance imaging, in a prospective study of 82 cases (53 fetuses and 29 children), the authors found that magnetic resonance should be the modality of choice for non-invasive post-mortem imaging in fetuses and children, as unenhanced computed tomography has limited value in detection of major pathology primarily because of poor-quality, non-diagnostic fetal images [118].

It appears that post-mortem magnetic resonance examinations can be reliably reported by a single radiologist, following a period of experience. Compared against conventional autopsy, the overall diagnostic accuracy was recently reported 89.6% across all cases, with high concordance 91.8% across most organ systems [119].

Although conventional autopsy remains the gold standard, the post-mortem non-invasive or less-invasive [120–122], imaging techniques, preferably associated with targeted tissue biopsy, represent an acceptable alternative when the previous is declined. However, the availability of trained personnel and appropriate medical equipment is very limited whereas large multicenter studies reporting similar encouraging data are still expected.

Case presentations

We will present in the following several cases different particularities that underline the necessity of perinatal autopsy.

Ultrasound morphological assessments were performed in the Prenatal Diagnostic Unit of the Emergency County Hospital, Craiova, Romania, by sonographers with extensive experience in first trimester genetic and mid-trimester anomaly scan. The acquisition of images was realized transabdominally and transvaginally, using probes from GE Voluson 730 Pro and Expert, GE Medical Systems, Kretztechnik, ZIPF, Austria. Post-mortem morphological examinations were performed in the Department of Pathology of the same Unit. Parental consent was obtained for all investigations. An extensive sequential segmental analysis of the fetuses was performed, as completely as possible, irrespective of the gestational age. In cases of first trimester fetuses, the small structures as the fetal heart were dissected under microscope.

Case No. 1

First case, 34-year-old primigravida, obese (body mass index – BMI 35 kg/m^2), was admitted in our Clinic for uterine contractions at the beginning of the third trimester of pregnancy (30 gestational weeks). This was also her first obstetrical evaluation.

The ultrasound examination (Figure 1) revealed polyhydramnios, absence of orbits, large cystic mass that

occupied the left part of thorax and abdomen and complex major cardiac malformation. Because of topography of the cystic mass, digestive obstruction was suspected with congenital diaphragmatic hernia. The polyhydramnios was considered secondary to the probable digestive obstruction. Regarding the major congenital heart disease, common arterial trunk or overriding aorta and pulmonary stenosis were suspected at ultrasound evaluation. The heart displacement secondary to the presence of the cystic mass in the left thorax have led to dextroposition, rotation, mass effect, and alteration of the anatomical rapports between heart chambers and great vessels, which made impossible an accurate diagnosis. Also, the obesity, the large amount of amniotic fluid and the improper gestational age for anomaly scan considerably altered the sonographic visualization.

A definitive diagnostic of the abnormalities was established only following the autopsy (Figure 2): orbits atresia, congenital heart disease – common arterial trunk, intestinal malrotation and bowel atresia, large diaphragmatic left defect with the herniation of an enlarged stomach into the thorax and severe pulmonary hypoplasia.

In our opinion, such complex cases benefit from the pathological examination for many reasons. Obviously, the ultrasound evaluation yielded major malformations. However, above-mentioned poor examination conditions severely impaired the examination and subsequently a comprehensive prenatal ultrasound diagnosis.

Regarding the congenital heart disease, common arterial trunk or overriding aorta and pulmonary stenosis were suspected at ultrasound evaluation. The autopsy established the final diagnosis – common arterial trunk.

The differential diagnosis of a thoraco-abdominal cystic mass may involve several anatomical systems, *e.g.*, cardiovascular, digestive, and urinary. It is impossible to establish prenatally the diagnosis of bowel atresia or intestinal malrotation by ultrasound or other imagistic technique. Although suspected at the ultrasound examination, the autopsy confirmed the digestive obstruction and revealed the nature of the pathology.

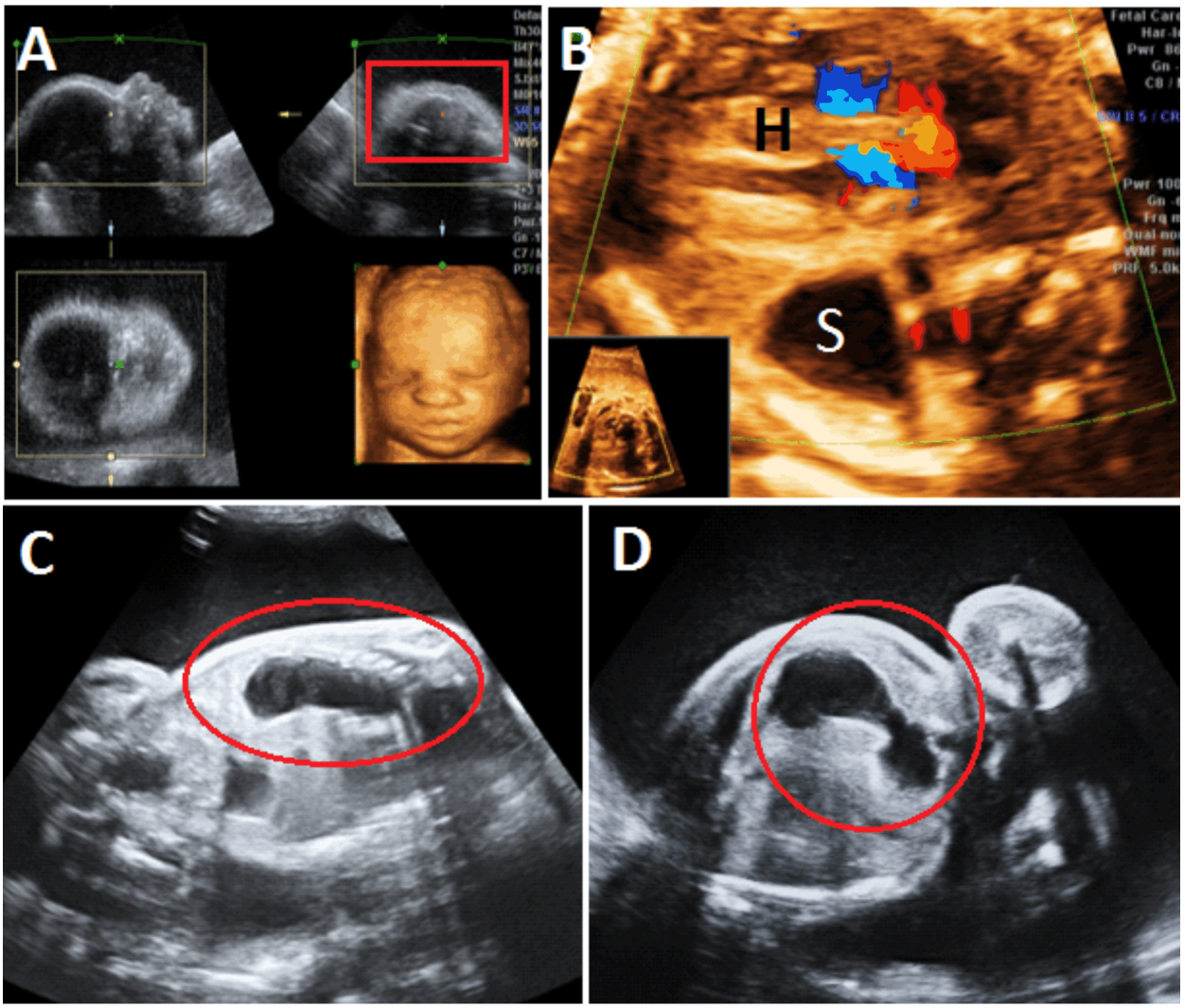

Figure 1 – ***Ultrasound evaluation of a multiple malformed fetus in the third trimester: (A) Absence of the orbits in 3D rendering of the fetal face (plane B, red rectangle); (B) Diaphragmatic defect suspected in axial view of the fetal thorax, because of the dextrocardia and the presence of a cystic mass in the thorax; (C) Large cystic mass extending in the abdomen and thorax, longitudinal view of the fetal trunk; (D) Axial view of the fetal abdomen showing an enlarged image of the stomach. S: Stomach; H: Hearth.***

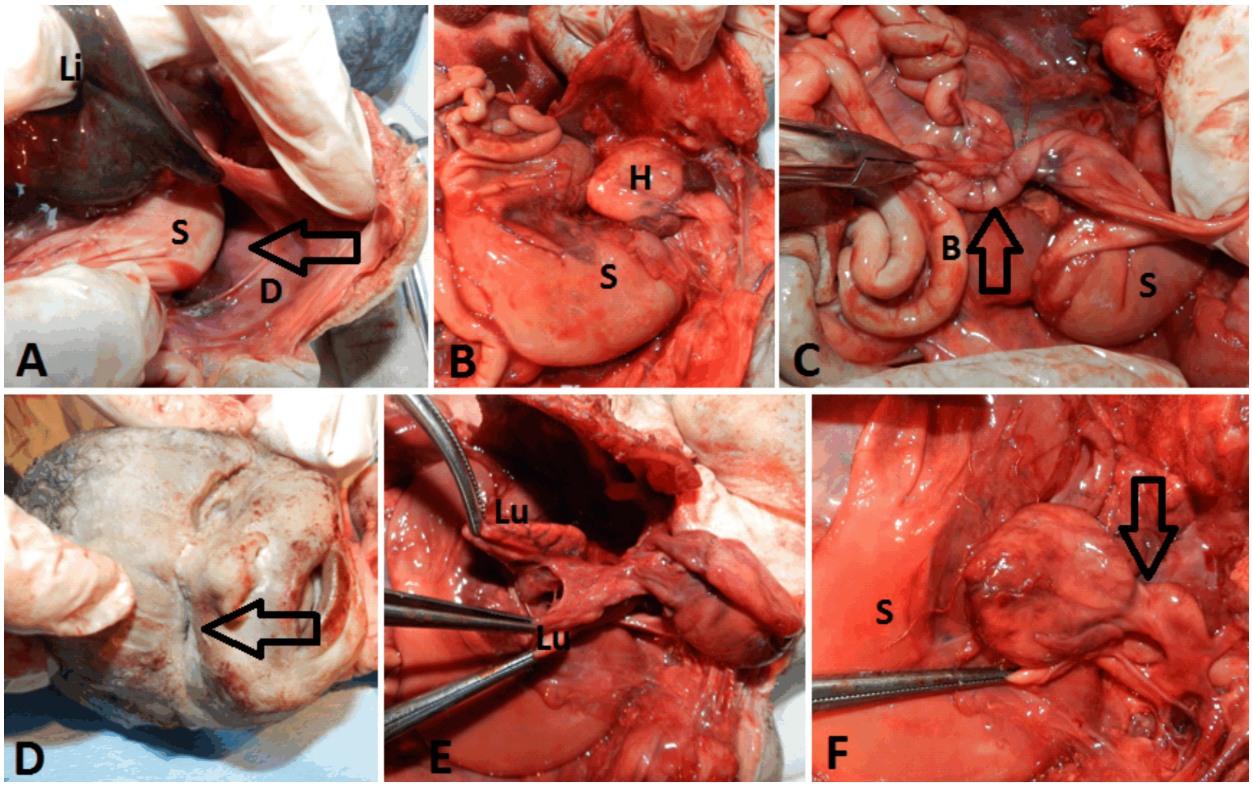

Figure 2 – ***Autopsy of a third trimester fetus (32 gestational weeks) that confirmed the major digestive and cardiac abnormalities suspected by ultrasound and established the cause and consequences of intestinal obstruction. Large diaphragmatic defect (A), with the herniation of an enlarged stomach into the thorax (B). Bowel malrotation with secondary intestinal obstruction, leading to digestive obstruction (C). Absence of the eye bulbs and impossibility to evidentiate the orbits at the traction on the eyelid (D). Pulmonary hypoplasia, with the presence of a small rudiment instead of the left lung, as a consequence of massive herniation of the stomach in the thorax (E). Common arterial trunk (F). Li: Liver; S: Stomach; H: Hearth; B: Bowel; Lu: Lung.***

Case No. 2

Second case, 26-year-old primigravida, low-risk pregnancy, first trimester assessment for combined test at 11 gestational weeks.

The ultrasonographic assessment (Figure 3) showed normal genetic markers but suspected atrio-ventricular septal defect. The patient was rescheduled within the next week for a team evaluation, in order to confirm the cardiac defect. The imagistic reassessment at 12 gestational weeks (Figure 3) did not confirm the septal defect; however, hypoplastic right heart syndrome was highly suspected, based on the enlarged right atrium, reduced filling of the right ventricle and reversed flow in pulmonary artery. All these abnormal features appeared normal at the initial evaluation. Also, negative *a*-wave was found at the *ductus venosus* assessment, although normal positive *a*-wave was evident at the previous evaluation. Normal (46, XX) karyotype was confirmed after chorionic villus sampling; however, the couple decided therapeutic abortion.

Following the termination of pregnancy, the autopsy confirmed the suspected diagnosis: hypoplastic right heart with intact septum, secondary to atretic tricuspid valve (Figure 4).

This case confirms that certain structural abnormalities develop during pregnancy. Major changes of the anatomical features may appear at the first trimester imagistic evaluations, therefore, the early anomaly scan should be performed at the end of the first trimester, if possible. Re-examination and team evaluations are important tools to lower the false positive rate of early anatomical scan, but also to establish an accurate diagnosis of a malformation, especially in the first trimester of pregnancy. Moreover, the autopsy could reveal supplementary abnormalities in early terminations of pregnancy that, due to the low gestational age, are missed at the imagistic examination.

Therefore, we suggest that early termination of pregnancy should benefit from the same attention regarding the pathological evaluation, because the ultrasound examinations are more likely to under- or over-diagnose fetal structural abnormalities. This is important as a quality control for the performance of early antenatal diagnosis and for parental counseling the parents regarding the risk of abnormalities in future pregnancies.

Case No. 3

Third case, 24-year-old primigravida, low-risk pregnancy, first trimester assessment for combined test at 12 gestational weeks. Normal amount of amniotic fluid and presence of bladder were noted (Figure 5).

At the second trimester anomaly scan (24 gestational weeks), the ultrasound evaluation found anhydramnios. Normal renal parenchyma could not be seen, but instead, large heterogeneous masses with echogenic and cystic areas, suggesting renal dysplasia. The renal arteries were evident at the color Doppler investigation. Also, a small image of bladder was transitory evident between the two umbilical arteries abdominal course (Figure 5).

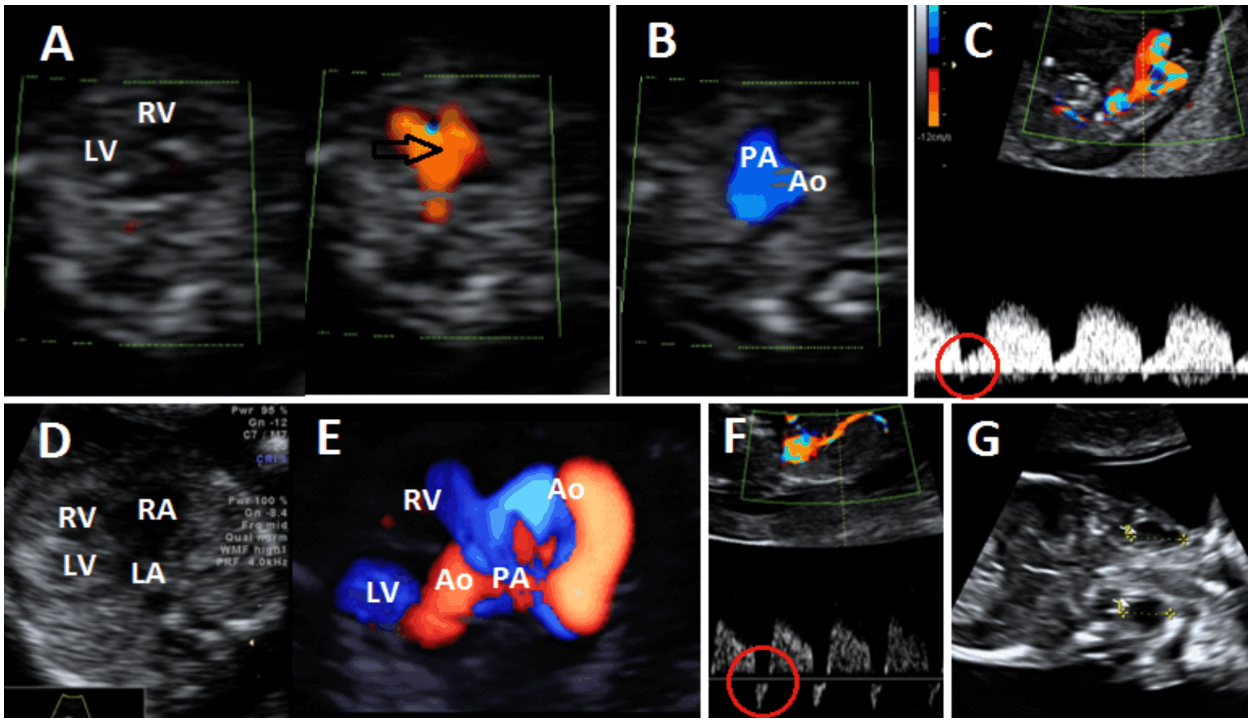

Figure 3 – *Ultrasound evaluation of the same fetus at 11 gestational weeks (upper row) and 12 gestational weeks (lower row): (A) Four-chamber view with atrio-ventricular septal defect suspected; (B) Normal flow in aortic and pulmonary arterial arches in three vessels and trachea view; (C) Positive a-wave at ductus venosus assessment; (D) Enlargement of the right atrium at the re-evaluation scheduled after one week; (E) 4D STIC (spatio-temporal image correlation) assessment showing reduced filling of the right ventricle and reversed flow in the pulmonary artery, suggesting tricuspid atresia with intact septum – hypoplastic right heart; (F) Inversed a-vawe at the ductus venosus evaluation; (G) Lateral cystic hygroma colli. LV: Left ventricle; RV: Right ventricle; LA: Left atrium; RA: Right atrium; PA: Pulmonary (ductal) arterial arch; Ao: Aorta.*

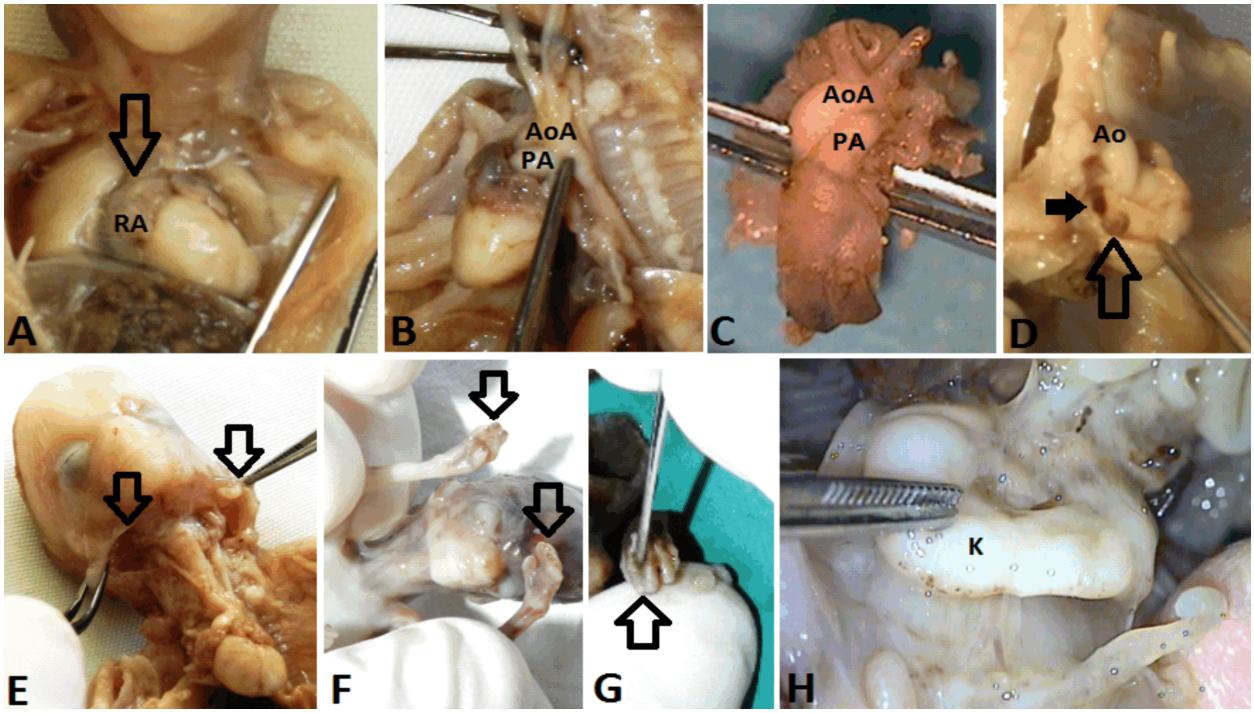

Figure 4 – *Autopsy of a first trimester fetus (12 gestational weeks) that confirmed major abnormalities suspected by ultrasound and completed the diagnosis with additional findings: (A) In early stages of development, the ventricular hypoplasia may not be evident – autopsy confirmed relatively equal ventricles with enlarged right atrium; (B) Normal aspect of arterial (aortic and ductal) arches; (C) Ventriculo-arterial concordance and crossing of the great vessels at the base of the heart; (D) Narrowed dysplastic right atrio-ventricular connection (open arrow) with normal aspect of foramen ovale (black arrow); (E) Cystic hygroma colli; Autopsy further diagnosed hands abnormality – clenched hands (F), syndactyly (G) and horseshoe kidneys (H). RA: Right atrium; AoA: Aortic arch; PA: Pulmonary artery; Ao: Aorta; K: Kidney.*

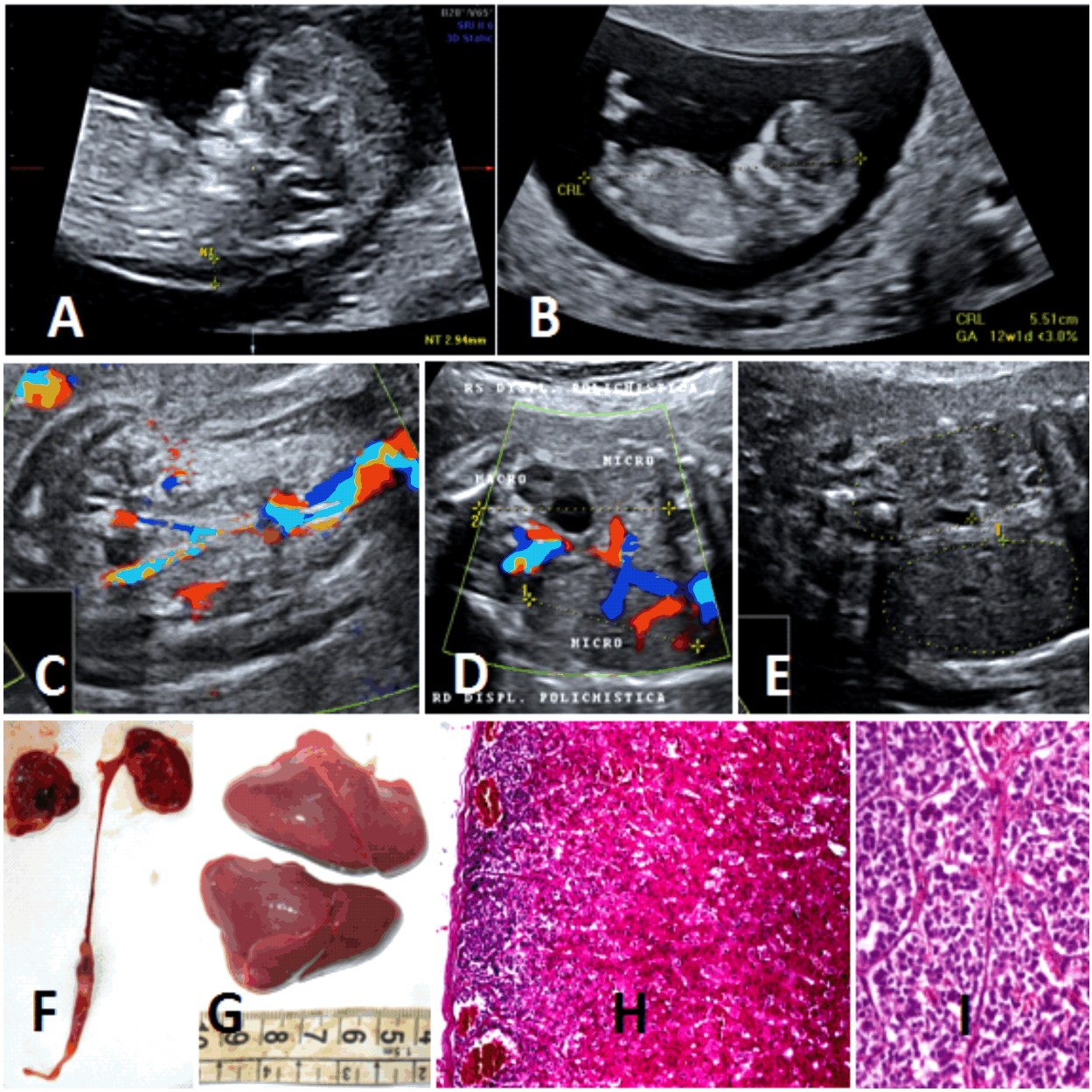

Figure 5 – ***Sequential prenatal scan of a fetus with bilateral suprarenal tumors. Upper row – first trimester (12 gestational weeks) findings: (A) Increased NT (nuchal translucency) measured in 3D volume because of persistent unfavorable position of the fetus; (B) Presence of a bladder image and normal amount of amniotic fluid. Lower row – second trimester (24 gestational weeks) findings: anhydramnios in the same fetus (C–E); (C) Color Doppler imaging of the umbilical arteries lateral to a transitory present small bladder; (D) Color Doppler imaging of renal arteries and large heterogeneous masses lateral to the fetal spine (4.5 cm); (E) Large latero-spinal masses suggested the diagnosis of enlarged dysplastic kidneys; (F) Pathological exam showing abdominal masses attached to the urinary tract with different aspect than normal or polycystic kidneys; (G) Measurement of the abdominal masses; (H and I) The histological assessment revealed congenital suprarenal hyperplasia. HE staining: ×40 (H); ×100 (I).***

Given the poor prognostic of the fetus, the couple elected termination. The autopsy showed abdominal masses attached to the urinary tract with different aspect than normal or polycystic kidneys. The histological examination yielded suprarenal hyperplasia replacing renal parenchyma. This finding significantly changes the counseling for future pregnancies regarding the recurrence risk.

This case underlines the importance of the autopsy and collateral investigations, as the histological study of samples collected during the pathological evaluation.

Conclusions

Nowadays, the information obtained by prenatal imagistic assessment of the pregnancy has become essential in the routine pregnancy care, and the detection of developmental anomalies has improved significantly. However, parents should be encouraged to accept the gold-standard pathological investigation and accurate perinatal autopsy protocol should be performed in all therapeutic terminations of pregnancy or stillbirths, in order to verify or improve the prenatal imagistic diagnosis. Parental

counseling for future pregnancies, the development of sonographic anomaly diagnostic and perinatal pathology, benefits from the close cooperation between ultrasonographers and pathologists. The collection of the tissue samples for further analyses should constitute an important step of the perinatal autopsy.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Maria Şorop-Florea and Nuţi Daniela Oprescu equally contributed to the manuscript.

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Corresponding authors

Ştefania Tudorache, Associate Professor, MD, PhD, Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40722–220 235, Fax +40251–502 179, e-mail: stefania.tudorache@gmail.com

Simona Vlădăreanu, Associate Professor, MD, PhD, Department of Obstetrics–Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy; Department of Obstetrics and Gynecology, "Elias" Emergency Clinical Hospital, 17 Mărăşti Avenue, Sector 1, 011461 Bucharest, Romania; Phone +40721–200 461, e-mail: simconst69@gmail.com

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