Classification of stillbirths in University Hospital of Split by relevant condition at death (ReCoDe) system

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CLASSIFICATION OF STILLBIRTHS IN UNIVERSITY HOSPITAL OF SPLIT BY RELEVANT CONDITION AT DEATH (RECODE) SYSTEM

Diploma thesis

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TABLE OF CONTENTS

1. INTRODUCTION 1

1.1. Newborn Terminology 2
1.2. Pregnancy Outcome 2
1.3. Maturity 4
1.3.1. Mature newborn 4
1.3.2. Premature newborn 5
1.3.3. Postmaturity 5
1.4. Weight 6
1.5. Epidemiology 6
1.6. Etiology 7
1.6.1. Maternal stillbirth risk factors 7
1.6.2. Fetal stillbirth risk factors 7
1.6.3. Placental stillbirth risk factors 8
1.6.4. Iatrogenic 10
1.7. Stillbirth Classifications 11
1.7.1. ReCoDe – Stillbirth Classification 11

2. AIMS AND HYPOTHESIS 14

3. MATERIALS AND METHODS 16

4. RESULTS 20

5. DISCUSSION 28

6. CONCLUSION 33

7. REFERENCES 35

8. SUMMARY 43

9. CROATIAN SUMMARY 45

10. CURRICULUM VITAE 47

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1. INTRODUCTION

1.1. Newborn Terminology

Definition of stillbirth and perinatal mortality in general can be confusing in terms of the terminology used among doctors and even throughout the medical literature. This confusion results from the fact that the viability of preterms changed over time as the pediatric intensive care units developed. For example, today in 2018 we are able to maintain the lifes of preterm infants as young as 20th week of gestation (w.g.) which was impossible just couple of years ago. As our medical knowledge and equipment continue to develop, some of the definitions surely will continue changing as the viability of preterms outside of the uterus will improve. Following definitions are based upon the National Center for Health Statistics of the Centers for Disease Control and Prevention and World Health Organization (1,2):

- Neonatal or newborn period describes the first 4 weeks (28 days) of life. It can be split into early- (<7 days) and late- (7-28 days) neonatal period.
- Perinatal period is commonly defined in two ways. First definition comprises the time span between 28th w.g. and early neonatal period (1st week). Second definition spans between 20th w.g. and 4th week of age after delivery (neonatal period).
- Infant period represents the first 365 days (1 year) of life.

1.2. Pregnancy Outcome

Any pregnancy will eventually terminate in a miscarriage, a stillbirth or ideally in a livebirth (Figure 1).

Miscarriage, or spontaneous abortion, describes pregnancy loss before the 20th w.g., where the fetus weights less than 500 grams and is without vital signs (e.g. pulse, respiration and umbilical cord pulse). The term "early miscarriage" is used if it occurs before the 16th w.g., whereas "late miscarriage" describes the same incidence after the 16th w.g.. Recurrent miscarriage, or habitual abortions, is defined as three or more miscarriages before the 20th w.g. (3).

Stillbirth, also known as fetal death or intrauterine fetal demise, is defined as the loss of pregnancy after 20th w.g., where the fetus weights more than 500 grams and is without vital signs. We can again differentiate between "early stillbirth" (20th until 27th w.g.) and "late stillbirth" (≥28th w.g.) (4).

In contrary to miscarriage and stillbirth, a livebirth describes any newborn who shows vital signs (pulse, respiration, umbilical cord pulse) after delivery, even if the newborn dies right after the delivery. If death of a live birth occurs within the first year of his or her life (<365 days) we call it an infant death. It is further subdivided into neonatal- (<4 weeks) and post

neonatal (≥4weeks) death. Neonatal death in turn is divided into early neonatal (<1week) and late neonatal (≥1st-4th week) death (5).

The term perinatal death is used when death occurs in the perinatal period, i.e between 28th w.g. and less than 7days of age after delivery. It covers late stillbirth (≥28th w.g.) plus early neonatal death (<7 days old). Sometimes the definition not only covers the late period of stillbirth but the entire stillbirth period (≥20th w.g.) and not only the early neonatal period but the entire neonatal period (1st-4th week of life), so that perinatal death is sometimes defined as death occurring anytime between 20th w.g. and the 4th week of age after delivery (6).

Stillbirth rate, neonatal- and perinatal mortality rates as well as infant mortality rate are counting the number of deaths in the respective time intervals per 1000 live births (7,8).

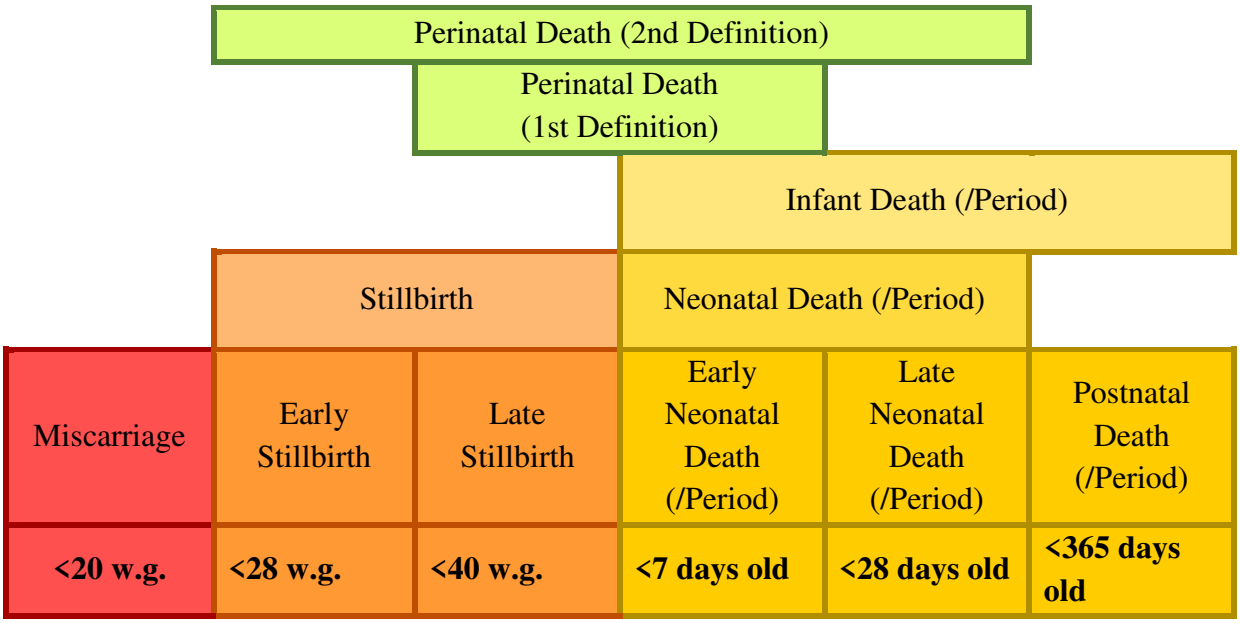

Figure 1. Overview of all periods of life and death related to the newborn (1–6).

1.3. Maturity

Maturity of a newborn is linked to the time of the delivery, so we can differentiate newborns who are born premature (<37th w.g.), mature (37th - 42th w.g.) and postmature (>42th w.g.).

1.3.1. Mature newborn

Physical signs of a healthy and mature newborn at 40th w.g. according to normograms include anthropometric measures, vital signs, laboratory diagnostics and physiological changes of the body (9,10):

Table 1. Physical signs of a healthy and mature newborn at 40th w.g. according to normograms

Anthropometry	Body Length:	48 cm – 53 cm
	Body Weight: Female	2.8 kg – 4.0 kg
	Male	2.9 kg – 4.2 kg
	Head Circumference:	33 cm – 37 cm
Vital Signs	Heart Rate:	120 – 160 beats per minute
	Respiratory Rate:	40 – 60 breats per minute
	Blood Pressure: Systolic	50 – 70 mmHg
	Diastolic	30 – 45 mmHg
	Temperature:	36.5°C – 37.5°C
Bilirubin	Direct (conjugated)	<1 mg/dl
	Total	<2 mg/dl
First urine and stool ("meconium")	Urine within 24 hours and meconium within 48 hours after delivery	
Weight loss in first 5 days of life	Maximal 7% of birth weight	
Hormonal influence	Breast buds in both genders Bloody mucoid vaginal discharge in female newborn due to maternal estrogen	
Posture	Flexed limb, good muscle tone	
Skin	Rosy / pink, some visible veins, subcutaneous fat present, *vernix caseosa*	
Body hair	Absent (most) or some thinned lanugo hair	
Auricular cartilage	Completely developed within pinna, naturally recoils after folded	
Breast	Visible and raised areola, 3-4 mm breast buds	
Male genitalia	Fully descended testes	
Female genitalia	Labia minora is covered by larger labia majora	
Plantar creases	At least covering anterior 2/3 of foot	
Nails	Reaching figertips	

1.3.2. Premature newborn

Prematurity is either due to preterm premature rupture of membranes (PPROM) or elective preterm delivery (11). The former, which describes a spontaneous rupture of amniotic sac before the onset of labor prior to 37th w.g., is most often caused by chorioamnionitis. The latter is usually indicated to prevent maternal and fetal morbidity or mortality, in cases such as gestational hypertension (preeclampsia, eclampsia, HELLP syndrome), intrauterine growth retardation (IUGR), hydrops, placental abruption and so on. On gross examination of the premature newborn you can find a red and wrinkled skin, often so thin that you can clearly see veins. There is a little amount of lanugo hair and subcutaneous fat. Plantar creases are not so prevalent so that the feet looks quite smooth. Instead of being raised, the areola is flat and without a breast bud. Also the ear will show only a little bit of cartilage and hence will not recoil when folded. Males will have an undescended testes while female might have a prominent clitoris and the labia minora won't be covered by the labia majora like in term newborns. Finally the posture will be hypotonic with extended limbs, just the opposite to the normotonic and flexed limbs in term newborns. Signs of severe jaundice due to the immature conjugation abilities of their immature livers and signs of severe anemia due to their immature bone marrow can be seen (12).

Autopsy examinations might reveal complications of their immature internal organs. These are hyaline membrane disease (HMD) in the lungs, necrotizing enterocolitis (NEC) in the intestines, intraventricular hemorrhage (IVH) and periventricular leucomalacia (PVL) in the brain, patent ductus arteriosus "Botalli" (PDA) and signs of iatrogenic damage in attempts to rescue the newborns life, which are barotrauma, pneumothorax (PTX), interstitial lung emphysema, bronchopulmonary dysplasia (BPD) and retinopatia of prematurity (ROP) (12).

1.3.3. Postmaturity

Postmaturity, sometimes known as "Clifford syndrome", are often caused by unkown factors, rarely fetal anomalies such as anencephaly seem to predispose the fetus for a prolonged pregnancy. These newborns have some typical macropscopic findings which are a dry, peeling and wrinkled skin with no lanugo hair and very little *vernix caseosa*, long fingernails, passed meconium and little subcutaneous fat (13).

A prolonged pregnancy can lead to placental insufficiency with secondary IUGR, decreased nutrition delivery leading to compensatory catabolism of subcutaneous fat and fetal anoxia

leading to release of meconium and cerebral palsy. Clifford described three stages of postmaturity, wherein higher stages indicate higher probability for adverse effects to the fetus (Table 2) (13,14).

Table 2. Stages for postmaturity by Clifford

Stage	Skin	Meconium Staining Placenta and Amniotic fluid	Meconium Staining Neonate
0	normal	none	none
1	dry, cracking, wrinkled, parchment like	none	none
2	dry, cracking, wrinkled, parchment like	present, green	present, green
3	dry, cracking, wrinkled, parchment like	present, yellow-green	present with nails affected, bright yellow

1.4. Weight

The weight of a newborn also reflects the maturity of a newborn but it can also reflect some pathological states.

A newborn is termed small-for-gestational-age (SGA) when his or her birthweight is below the 10th percentile for gestational age (i.e. the weight is always age depended and is compared to other newborns of the same gestational age and of the same gender).

Appropiate-for-gestational-age (AGA) is used when the birthweight is between the 10th and 90th percentile for gestational age.

Large-for-gestational-age (LGA) is used when the birthweigth is above 90th percentile for gestational age (15).

1.5. Epidemiology

Worldwide there are over 3.2 million stillbirths occurring every year (2). About 98% of them occur in low- and middle-income countries. 75% occurred in South Asia and Sub-Saharan Africa and 60% occurred in rural families from these areas. This reflects a similar distribution

of maternal deaths (16). The incidences are as high as 32 stillbirths per 1000 births in South Asia and Sub-Saharan Africa whereas it is below 5 stillbirths per 1000 births in high-income countries (17).

The greatest time of risk seems to be the intrapartum period, the time during delivery. In this period 10% (developed countries) to 59% (south Asia) of all stillbirths occur. We also need to be aware of the fact that most stillbirths are uncounted in local and global data collection systems, so that the true numbers might be by far higher than we think.

Tackling stillbirths is still not among the top priorities even in high-income countries. This is probably due to the missing systematic approach on the numbers and causes of stillbirths.

1.6. Etiology

The causes for stillbirth can be topographically categorized into maternal, fetal, placental and iatrogenic (18). The most common risk factors for stillbirths in developing countries include the lack of a skilled attendant at delivery, low socioeconomic status, poor nutrition status, prior stillbirths and advanced maternal age (19).

1.6.1. Maternal stillbirth risk factors

Abnormalities of the reproductive organs and systemic diseases can physically and functionally impair the physiological development in utero. These include septate uterus, uterine leiomyomas, uterine adhesions, cervical incompetence, uterine rupture, diabetes mellitus, hyperthyroidism, hypothyroidism, genetic disorders, infections, hypercoagulability (e.g. antiphospholipid syndrome), smoking, hemoglobinopathies and prolonged pregnancy (>42 w.g.) (20).

1.6.2. Fetal stillbirth risk factors

Chromosomal abnormalities (Figure 2), congenital anomalies, multiple gestations, IUGR, genetic abnormality, infection (e.g. Parvovirus B19, Cytomegalovirus, Listeria Monocytogens), hydrops fetalis (e.g. Rhesus incompatibility) and direct mechanical trauma to mothers abdomen (20).

Figure 2. Macereted male fetus with Edwards syndrome demonstrating following gross findings: skin slippage and discoloration, cleft palate and lip, umbilical cord hypertorsion, overlapping of the fingers on both hands and so called "rockers foot". (Figure taken from the mentor's archive)

1.6.3. Placental stillbirth risk factors

Cord accident, placental abruption, placental previa, vasa previa, premature rupture of membranes (PROM), fetomaternal hemorrhage, placental insufficiency, gestational hypertension, preeclampsia, eclampsia and HELLP syndrome (20).

The term gestational hypertension or sometimes known as "hypertensive pregnancy disorders" can be broken down into pregnancy-induced hypertension and pregnancy-independent hypertension according the American College of Obstetricians and Gynecologists (21).

Pregnancy-induced Hypertension describes the onset of hypertension in the pregnant female after the 20th w.g. while she must have been normotensive until the 20th w.g. We can describe four clinical pictures which in reality are just a contuinity of the same pathology, i.e. arterial hypertension (Table 3).

Table 3. Clinical presentation of pregnancy induced hypertension

Gestational-Hypertension	New onset blood pressure >140/90 mmHg after the 20th w.g. (i.e. normotensive until 20th w.g.) while having no proteinuria
Pre-eclampsia	Gestational-Hypertension (see above) + at least one of the following signs: proteinuria, liver and/or renal and/or neurological impairment, changes in complete blood count
Eclampsia	Pre-eclampsia + Tonic-clonic seizures
HELLP syndrome	Pre-eclampsia + "**H**emolysis, **E**levated **L**iver Enzymes, **L**ow **P**latelet Count", i.e. low erythrocytes resulting in anemia, low thrombocytes resulting in petechia and liver damage resulting in high AST and ALT, high ammonia, low coagulation factores, low albumin, etc.

Although gestational hypertension manifests as a maternal disease it is assumed that it is caused by different pathophysiological mechanisms originating from the placental tissue, fetus and mother.

Three pathophysiological mechanisms are often cited in this regard: defective throphoblast invasion or uterine spiral arteries, maternal systemic vasoconstriction and maternal systemic endothelial dysfunction (22). Any of these three causes has the ability to cause maternal vasoconstriction and microthrombosis, both of which will impair end-organ perfusion and ultimately lead to organ damage (Figure 3).

Furthermore any of these three causes will lead to chronic placental hypoperfusion which in turn can lead to (IUGR).

Figure 3. Chronic placental hypoperfusion due to a pregancy complicated with pre-eclampsia. Cut sections show multiple infarctions. (Figure taken from the mentor's archive)

Pregnancy-independent hypertension can be split into "Chronic arterial hypertension", when the hypertension is already present before 20th w.g. and "Superimposed preeclampsia", when chronic arterial hypertension (see above) goes along with the diagnosis of preeclampsia after 20th w.g. (21).

1.6.4. Iatrogenic

Amniocentesis, chorionic villus biopsy, medicaments, live vaccines and ionizing radiation can be true causes of fatal pregnancy outcome (18,21).

1.7. Stillbirth Classifications

A study conducted by Jason *et al.* found out that newer classification system reduced the number of stillbirths previously classified as "unexplained" (23). While previous methods of classifications (e.g. Wigglesworth classification) resulted in up to 66% of stillbirths being classified as unexplained, a new classification system called "Relevant Condition at Death (ReCoDe)" is reducing this same number to 15%. This study also found out that fetal growth restriction was the single largest category of conditions associated with stillbirth and it was found in the majority of the cases previously classified unexplained.

Yet another study by Vicki *et al.* with the title "An evaluation of classification systems for stillbirth" compared six different classification systems for stillbirths (24). These were Amended Aberdeen, Extended Wigglesworth, PSANZ-PDC, ReCoDe, Tulip and CODAC stillbirth classifications. Three of the four outcome measures were the ability to retain the important information about the death by the classification system ("Infokeep"), the ease of use of the system ("Ease") and the proportion of unexplained stillbirths. They concluded that CODAC performed best (highest score) followed by PSANZ-PDC and ReCoDe, whereas Aberdeen and Wigglesworth did not perform so good and even demonstrated highest proportion of unexplained stillbirths, hence both of these systems were not recommended for future use.

1.7.1. ReCoDe – Stillbirth Classification

The ReCoDe Classification system classifies stillbirths by “Relevant (Re) Condition (Co) at Death (De)", hence ReCoDe. It is used exclusively for stillbirths and it tries to identify and categorize the conditions which existed at the time of death in-utero. This new system was developed by the Perinatal Institute and its goal is to find out relevant clinical conditions that are associated with stillbirths (23,25). Furthermore it tries to put light on stillbirths that are categorized as "unexplained" by conventional classification systems.

Its categories are anatomically oriented, it starts with the fetus and all other categories are found progressively more distal to the fetus. Overall there are nine categories in alphabetic order (A to F), each of these categories have subcategories which describe pathophysiological conditions and are listed in numerical order. For example, category "C. Placenta" (anatomic description) has five sub-categories, one of which is "5. Abruption" (pathophysiologic description), i.e. detachment of the placenta from the uterine wall before the onset of the labor.

This system attempts to find out "what" caused the stillbirth, instead of "why". You can code multiple categories, whereas primary condition is always put highest in the list for each

stillbirth when multiple condition were presents. Detailed guidelines describe how to use the ReCoDe classification (Table 4) (25).

Table 4. ReCoDe Classification, anatomical categories (left, alphabet) with pathophysiological subcategories (right, numbering)

(A) Fetus	1. Lethal congenital anomaly 2. Infection 2.1 Chronic (e.g. TORCH) 2.2 Acute 3. Non-immune hydrops	4. Iso-immunisation 5. Fetomaternal haemorrhage 6. Twin-twin transfusion 7. Fetal growth restriction* 8. Other
(B) Umbilical Cord	1. Prolapse 2. Constricting loop or knot†	3. Velamentous insertion 4. Other
(C) Placenta	1. Abruptio 2. Praevia 3. Vasa Praevia	4. Placental insufficiency /infarction‡ 5. Other
(D) Amniotic fluid	1. Chorioamnionitis 2. Oligohydramnios†	3. Polyhydramnios† 4. Other
(E) Uterus	1. Rupture	2. Other
(F) Mother	1. Diabetes 2. Thyroid diseases 3. Essential Hypertension 4. Hypertensive diseases in pregnancy	5. Lupus/Antiphospholipid Syndrome 6. Cholestasis 7. Drug abuse 8. Other
(G) Intrapartum	1. Asphyxia	2. Birth Trauma
(H) Trauma	1. External	2. Iatrogenic
(I) Unclassified	1. No relevant condition identified	2. No information available

* Defined as < 10th customised weight-for-gestation percentile

(calculator: www.gestation.net/centile)

† If severe enough to be considered relevant
‡ Histological diagnosis

Figure 4. Anastomoses between the circulations of the two fetuses in the monochorionic placenta. The "donor" (bottom) twin is donating his blood to the "recipient" (top) twin, so that the "donor" looks anemic and pale while the "recipient" looks polycythemic and red. (Figure taken from the mentor's archive)

2. AIMS AND HYPOTHESIS

Our hypothesis is that the results of the presented study will be in accordance to the developed countries literature in the terms of the most common stillbirth causes. Likewise, the pathological investigations, including both autopsy findings and placental pathohistological reports, will yield further information relevant to the cause of death in stillbirths, especially those classified as "*mors fetus*" by clinicians.

3. MATERIALS AND METHODS

The presented research is a retrospective study over a time span of 7 years (from January 1st 2010 till December 31st 2016). In that period 261 cases of perinatal deaths were recorded at the Pathology Department, University Hospital of Split. Out of those 261 cases, we only selected the stillbirth cases, which were 115 in total. The collected data included pathological data, both fetal autopsy reports and placental pathological reports from pathology archive when available. Besides pathological data clinical information were taken from the autopsy request form derived from the Gynecology and Obstetrics Department, University Hospital of Split.

Complete fetal autopsy comprised external and internal gross examination with tissue sampling for histology and various microbiology samples when required. External gross examination included anthropometric measurements, maceration grading, estimating the general appearance (i.e. maturity and external anomalies) and finally taking skin sample for cytogenetics if needed. Furthermore, photographs and radiographs are taken when necessary. Internal gross examination included examination of the abdomen, neck and thorax and finally the skull. All obtained organs were weighted and all anomalies were recorded.

The placental pathologic examination compromised a throughout gross and histologic examination of the placenta by the attending perinatal pathologist. Most important characteristics were the placental weight, membrane insertion, dimensions of the insertion site of the placenta and umbilical cord (length, diameter, and coiling pattern). The histologic samples were taken from the membranes (amnion and chorion), umbilical cord and placental parenchyma.

The clinical information were given by the respective doctors present at time of delivery and specialists that were consulted as needed and includes various diagnosis related to both child and mother that clinician considered valuable for the autopsy and final diagnosis.

We manually collected all data and summarized them in a table with the use of Excel 2016 software. Following data were collected from autopsy report: whether or not it was a stillbirth, gender, gestational age and final pathological diagnosis.
Furthermore, we summarized the collected autopsy findings into seven categories and allocated each stillbirth case into one, the most significant category. The categories were as follows:

1. **Signs of hypoxia**: Hemorrhage into thymus, lungs and heart, congested internal organs and aspiration of amniotic fluid on light microscopy.

2. **Infection**: inflammatory cell infiltrates in various organs or tissues on light microsopy, viral, bacterial, fungal and protozoal identification from lung swabs, and positive microbial cultivation by the microbiology department.

3. **Malformations**: including isolated malformation as heart congenital defects or malformations as part of a syndrome.

4. **Maceration**: *Macerare* (latin, meaning "soften by soaking") occurs to fetus in the uterus after death due to autolytic enzymes in a sterile environment, i.e. amniotic cavity. "*mors fetus intrauterine*" or "*mors fetus prepartum*“ means fetal death during pregnancy. Here we expect signs of maceration! "*Mors fetus intrapartum*" means fetal death during delivery. In this case we don’t expect signs of maceration. Maceration has various stages depending on the duration of the stillbirth beeing in the amniotic cavity. It can be divided into 4 stages (Table 5) (26,27).

Table 5. Stages of maceration depending on the time elapsed since the fetal death

Grade of Maceration	Physical Signs	Duration of intrauterine death
Stage 0	Parboiled skin, reddened skin	<8 hours
Stage 1	Skin slippage, skin peeling (epidermis detaches from dermis)	>8 hours
Stage 2	heavy peeling skin, red serous effusion in chest and abdomen	2-7 days
Stage 3	yellow-brown liver, mummification	>7 days

5. **Umbilical cord** pathology included any finding differing from normal cord anatomy. The normal cord has 3 blood vessels (2 arteries and 1 vein) embedded in a loose myxoid tissue called Whartons jelly, is encased by single layer of amnion, which is continuous with the surface of the placenta and the fetal skin, is 55-65cm length at term (most length gained by 28th w.g.) and has 2-2.5cm diameter with loose and counter-clockwise twist. One twist is present per 5cm, related to fetal movement. Any insertion site except "velamentous" is consdered normal (28).

6. **Signs of Hydrops**: edema of skin, mucosa and internal organs, as well as congestive heart failure and signs of anemia.

7. **Rhesus (Rh) - isoimmunization** is a mainly clinical diagnosis, however a pathologic diagnosis of Rh-issoimunisation can be made when signs of anemia and hydrops are found at the autopsy and when there are anamnestic data of rhesus negative mother giving birth to rhesus positive child, with history of previous pregnancy to a rhesus negative child which lead to maternal immunization and IgG production which can cross the placenta.

The pathological diagnosis were also allocated into one of the ReCoDe groups and subgroups in accordance to Table 4.

Clinical information were listed on the accompanied autopsy request form. For the purpose of this study we summarized them into ten categories and allocated each stillbirth case into one category. The categories are as follows:

1. **Mors fetus** ("fetal death")
   this category was assigned to the case that had only "*mors fetus*" listed on the autopsy request form.
2. **Prematurity + Mors fetus**
3. **Malformations**
4. **Placental abruption**
5. **Infection**
6. **Rhesus (Rh) - isoimmunization**
7. **Hydrops**
8. **Umbilical cord strangulation or knot**
9. **Maternal disease**
10. **Twin pregnancy**

Autopsy findings and ReCoDe groups were determined for those stillbirths with the vague clinical information "*mors fetus*".

Furthermore ReCoDe groups were stratified according to the maturity of the stillbirths (preterm vs. term stillbirth) as well as according to the time period when the fetus died (early vs. late stillbirth).

Statistical analysis was done by the MedCalc software (MedCalc software, Ostend, Belgium) using the chi-squared-test. Statistical significance was set at $P<0.05$.

4. RESULTS

The study included 115 stillbirths through the timespan of 7 years (from January 1st 2010 till December 31st 2017). 60% of stillbirths were males, which was statistically significant (P=0.032; $\chi 2$=4.6; DF=1). Majority of stillbirths (73%) were over 28 weeks of gestation, therefore classified as late stillbirth, and 77.4% of all cases were preterm babies. Both findings were statistically significant (P<0.001; $\chi 2$=24.426; DF=1 and P<0.001; $\chi 2$=34.513; DF=1, respectively).

Causes of stillbirth according to ReCoDe classification are presented in Table 6. The most common category was amniotic fluid and all of the cases under this category were diagnosed as chrorioamnionitis, while the least common categories were uterus (only one case diagnosed as placenta accreta) and two cases categorized as mother (one case was eclampsia and the other was essential hypertension). Presented findings were statistically significant (P<0.001; $\chi 2$=41.130; DF=6).

Table 6. Causes of stillbirth according to ReCoDe classification. Order is according to ReCoDe classification by anatomy

Categories	**N (%)**	***P****
Fetus	23 (20%)	
Umbilical cord	22 (19.1%)	
Placenta	17 (14.8%)	
Amniotic fluid	27 (23.5%)	<0.001
Uterus	1 (0.9%)	
Mother	2 (1.7%)	
Unclassified	23 (20%)	

*chi-squared test

ReCoDe categories and their subgroups are presented in Table 7.

Table 7. Causes of stillbirth by ReCoDe categories and their subgroups. Order is according to ReCoDe classification by anatomy

Category	**Subgroup**	**N (%)**	***P****
Fetus	Congenital anomaly	14 (60.9%)	<0.001
	Infection	3 (13 %)	
	Non-immune hydrops	2 (8.7%)	
	Rh iso-immunisation	1 (4.3%)	
	IUGR	2 (8.7%)	
	Twin-twin transfusion	1 (4.3%)	
Umbilical cord	Loop or knot	14 (63.6%)	0.200
	Other	8 (36.4%)	
Placenta	Abruption	7 (41.2%)	0.466
	Other	10 (58.8%)	
Amniotic fluid	Chorioamnionitis	27 (100%)	
Uterus	Placenta accreta	1 (100%)	
Mother	Hypertensive disorders in pregnancy	1	
	Essential hypertension	1	
Unclassified	No relevant condition found	14 (60.9%)	0.297
	Insufficient information	9 (39.1%)	

*chi-squared test

The most common subgroup in the fetus category was congenital anomaly and the least common were Rh iso-immunisation and twin-twin syndrome, which was statistically significant (P<0.001; $\chi 2$=41.130; DF=6). Congenital anomaly subgroup included following: multiple malformations, Edwards syndrome, congenital arthrogriposis, osteohondrodysplasia, preterm closure of ductus arteriosus, anencephaly, triploidy and urethral valve stenosis.
In the umbilical cord category there were two subgroups: 14 cases of umbilical cord loop or knot and 8 other cases (6 umbilical cord hypertorsions and 2 velamentous insertions), the result wasn't statistically significant (P<0.200; $\chi 2$=1.636; DF=1).
The most common subgroup in the placenta category was "other" which included 5 cases of maternal vascular malperfusion (MVM), one case of MVM combined with fetal vascular malperfusion (FTV), one case of isolated FTV, two cases of FTV combined with vilitis of unknown etiology (VUE), and one retroplacental hematoma. The difference between subgroups in the placenta category wasn't statistically significant (P=0.466; $\chi 2$=0.529; DF=1). In the mother category only two cases were reported and in the uterus category only one case was reported. All of the cases recorded in the amniotic fluid category were of chorioamnionitis. In the unclassified category there were 14 unexplained cases while 9 cases didn't have enough information needed for classification.

Clinical information and autopsy findings are given in Table 8.

Table 8. Clinical information and autopsy findings

Clinical information	**N (%)**	***P****	**Autopsy findings**	**N (%)**	***P****
Preterm	45 (39.1%)		Signs of hypoxia	42 (36.5%)	
Mors fetus	22 (19.1%)		Maceration	32 (27.8%)	
Umbilical cord strangulation or knot	10 (8.7%)		Fetal malformationes	15 (13%)	
Fetal malformation	9 (7.8%)		Umbilical cord abnormalities	12 (10.4%)	
Placental abruption	9 (7.8%)	<0.001	Infection	10 (8.7%)	<0.001
Twin pregnancy	9 (7.8%)		Hydrops	3 (2.6%)	
Syndrome of intraamniotic infection (SIAI)	5 (4.3%)		Rh iso-immunisation	1 (0.9%)	
Maternal disease	3 (2.6%)				
Non-immune hydrops	2 (1.7%)				
Rh iso-immunisation	1 (0.9%)				

*chi-squared test

The most common clinical information for stillbirth was preterm baby (P<0.001; $\chi 2$=136.391; DF=9), while the most common autopsy finding was signs of hypoxia (P<0.001; $\chi 2$=83.861; DF=6).

When the only clinical information on autopsy request form was *"mors fetus"* then the most frequent autopsy finding was "Signs of hypoxia", which was statistically significant (P<0.001; $\chi 2$=19.091; DF=6), while the most common assigned ReCoDe group was "Unclassified" but this wasn't statistically significant (P=0.306; $\chi 2$=4.818; DF=4) (Table 9.)

Table 9. Autopsy findings and ReCoDe groups of stillbirths with clinical information "*mors fetus*". Order of ReCoDe groups is according anatomy

Autopsy finding	**N (%)**	***P****	**ReCoDe group**	**N(%)**	***P****
Signs of hypoxia	14 (63.6%)		Fetus	3 (13.6%)	
Maceration	5 (22.7%)		Umbilical cord	4 (18.2%)	
Malformations	2 (9.1%)	<0.001	Placenta	5 (22.7%)	0.306
Umbilical cord	1 (4.5%)		Amniotic fluid	2 (9.1%)	
			Unclassified	8 (36.4%)	

*chi-squared test

ReCoDe groups according to maturity of stillbirths are presented in Figure 5. The most common group in the preterm stillbirths was that of amniotic fluid while in the term stillbirths the most common ReCoDe groups were unclassified and umbilical cord. The findings were statistically significant (*P*=0.051; $\chi 2$=12.947; DF=6).

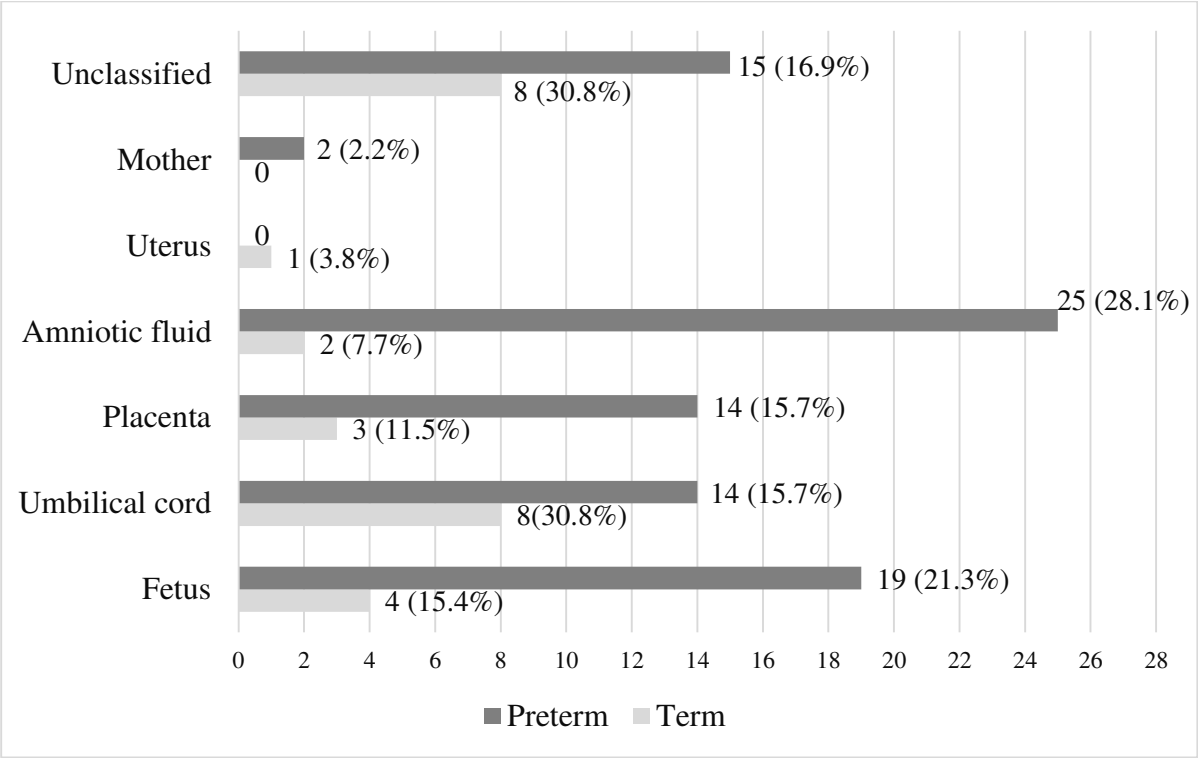

Figure 5. Prevalence of stillbirths in ReCoDe groups according to maturity of stillbirths. Preterm (N=89) and Term (N=26) stillbirths were allocated to ReCoDe categories by their cause of death (qui-squared test; *P*=0.051).

Figure 6 presents ReCoDe groups according to early and late stillbirth. The most common ReCoDe group among the early stillbirths was amniotic fluid, while in late stillbirths umbilical cord and unclassified were the most common ReCoDe groups. There wasn't statistically significant difference between early and late stillbirths according to ReCoDe groups (*P*=0.102; $\chi 2$=10.577; DF=6).

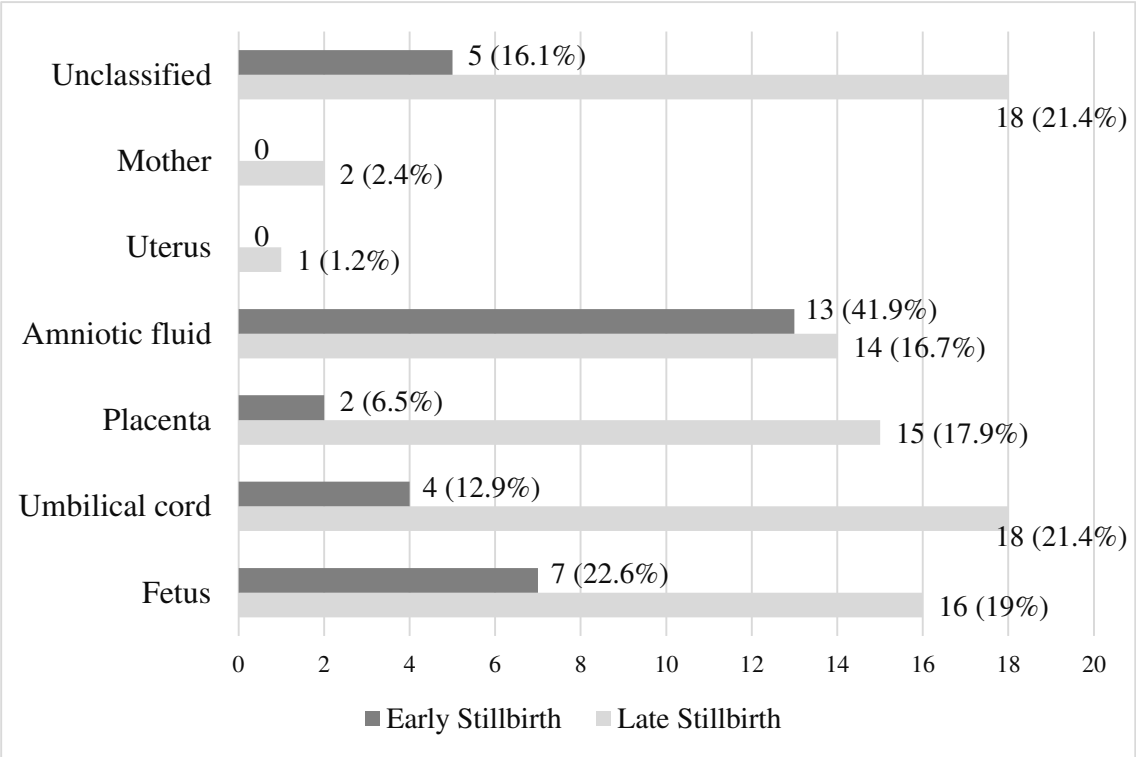

Figure 6. Prevalence of stillbirths in ReCoDe groups according to early and late stillbirths. Preterm (N=31) and Term (N=84) stillbirths were allocated to ReCoDe categories by their cause of death (qui-squared test; *P*=0.102).

5. DISCUSSION

A paper published in 2016 in the Lancet has shown that Croatia had a low stillbirth rate in 2015 (2 per 1000 births) compared with other high-income countries, for example: Germany (2.4/1000), Sweden (2.8/1000), UK (2.9/1000), USA (3.0/1000), Canada (3.1/1000), France (4.7/1000) and neighboring Bosnia (5.4/1000). Lowest stillbirth rate in 2015 was present in Iceland (1.3/1000) (29).

Despite the fact that the true scale of stillbirth incidence is unknown because of underreporting of stillbirth cases due to several reasons, those who are being reported are often devoid of an in-depth clinical investigation that determines the etiology as the cause of death (30–32).

Almost 3 million couples or families will be affected by third-trimester stillbirths every single year (17,33–35). In developed countries, early stillbirth cases (between 22th and 28th w.g.) might represent more than a 30% of these losses but are hardly ever counted in developing countries (35–37). The Lancet's Series entitled "Who counts?" is covering this topic about vital registries and their importance for the human rights of every single stillborn baby (38).

Stillbirth would rank fifth before diarrhoea, HIV/AIDS, tuberculosis, traffic accidents, and any form of cancer when compared with all the leading global causes of death in all age groups (39).

Most of the time the stillborn baby is known and mourned by the parents only (40,41). Following a stillbirth, the affected women often feel responsible for the death of their child and too often feel they are blamed by their husbands (42,43). One in five mothers develop long-term depression, anxiety or post-traumatic stress disorder (PTSD) (41,44,45). Even fathers are affected by negative psychosocial consequences (46). Etiologies leading to stillbirth are often associated with conditions that are ultimately lifethreatening to women's health. These can be obstetric emergencies like obstructed labour, infections like malaria, syphilis, chorioamnionitis or diseases like pre-eclampsia. Hence it it cruicial to identifiy them with the help of sensitive classification system like ReCoDe in order to adress and prevent them in future pregnancies. However, stillbirths are still not included in the major international measures of disease burden, such as the Millennium Development Goals or the Global Burden of Disease estimates, as a component of disability-adjusted life-years (DALY) (47). Under-reporting of stillbirths is caused by poor health surveillance and inconsistent definitions worldwide. Yet another reason is related to the topic of abortion (48,49). This means, in order to count a loss as a death we need to grant moral status to the life that has been lost. But in most countries throughout the

world only a baby who is born alive, meaning who breathes before death, is considered an individium by law. Consider a baby who is born alive at 35th w.g., taking few breaths but dies a few hours later is counted as a neonatal death and registered accordingly as "one life lost". However, a stillbirth at 35th w.g. occuring during delivery are not typically classified as deaths in many countries. So the question that emerges is - why is it that a 35 week old stillborn baby and the 35 week old preterm, who dies of respiratory failure hours after delivery in the pediatric-intensive-care-unit, both of them beeing developmentally indistinguishable, are looked upon differently? Why do we have this paradox approach in our mortality statistics?

Considering all of these issues it it necessary to call for inclusion of stillbirth as a recognised outcome in all relevant international health reports and initiatives. Also every country should develop and implement a plan to improve maternal and neonatal health. This should include the reduction of the stillbirth incidence and to count stillbirths in their vital statistics and other health outcome surveillance systems. Further investment in stillbirth-related research is needed. In particular research aimed at identifying and addressing barriers to count and systematically categorize stillbirths according to their cause of death.
To achieve a reduction in stillbirth rate coordinated action will be needed by many players including governments, WHO, other international health organisations, foundations, research institutes and professional and non-governmental organisations.

Alternative classification system for stillbirths are “Perinatal Society of Australia and New Zealand-Perinatal Death" (PSANZ-PDC) and "Causes of Death and Associated Conditions" (CODAC). The previously mentioned study comparing six different classification systems for stillbirth showed that PSANZ-PDC and CODAC performed a little better than ReCoDe in regards to their ability to retain the important information about the death and the ease of use of the system (24). However we choose the ReCoDe over PSANZ-PDC and CODAC classification system for stillbirth in our study because other studies have shown that the proportion of stillbirths classified as unexplained was less with ReCoDe compared with PSANZ-PDC or CODAC (50,51).

One of the biggest problem we faced was about the clinical diagnosis "*mors fetus*". It was the second most clinical diagnosis given by the clinicians accounting to about 19%. "*Mors fetus*" as the cause of death, which means nothing but "dead fetus" in latin without further information, is very unspecific and gives absolutely no clue about what caused or contributed to the death of the fetus neither to the pathologist who performs the autopsy nor to the family

who lost the child. Ultimately it is of zero help in summarizing etiologies of stillbirths via statistical analyses on a larger scale in order to combat these causes of stillbirth on a global and local level. Our study has shown that the subsequent pathological investigations, including fetal autopsy and placental reports, could yield more specific findings that might help understanding and determining the cause of death among the cases classified as "*mors fetus*" by clinicians.

Whenever clinicians reported "*mors fetus*" as the cause of death, despite the fact that the most common ReCoDe group for this clinical diagnosis was "unclassified", we could still find more specific pathological findings. These were signs of hypoxia (63.6%), maceration (22.7%), malformation (9.1%) and umbilical cord pathology (4.5%). In this case, two malformations were noted on autopsy and both of them were preterm closure of ductus arteriosus, a malformation which wouldn't be discovered without autopsy. Likewise in 22.7% of fetuses with "*mors fetus*" designation pathologic placental findings were observed, including both types of vascular malperfusion (fetal and maternal) indicating placental hypoxia.

Our study has shown that we had a significant predominance of the male stillbirth (60%) over female stillbirth (40%) over the time period of 2010 until 2016 at our hospital in Split. This is in accordance with a systematic review from 2014 conducted on more than 30 million birth outcomes that were reported in observational studies (52). This study found out that male fetuses have about 10% higher risk than female fetuses. The excess risk of the male sex in pregnancy is comparable to smoking which equates to an additional 100000 male stillbirth cases globally every year.

We found out that stillbirths after 28th w.g. (late stillbirth) outnumber the early stillbirths count by 73% vs. 27%, respectively. But unlike the correlation of sex with stillbirth this is not in accordance to studies found in the literature. For example, a study from 2015 by MacDorman *et al.* "Trends in Stillbirth by Gestational Age in the United States, 2006–2012" found out that majority of stillbirth cases occur before the 28th w.g., these are classified as early stillbirths (53).

Although many studies suggest that infection related stillbirth are quite rare in high-income countries but tend to occur more in post-term stillbirths and low-income countries (54–61), we have found out that according the ReCoDe classification chorioamnionitis was indeed the most common cause of death at our hospital. However studies found out that chorioamnionitis was present in 94% of placentas which were delivered at 21-24th w.g. indicating that these early stillbirths almost always were associated with chorioamnionitis (62).

Further investigations should determine the reasons that are present locally in Split that lead to chorioamnionitis in order to counteract them. Possible etiologies for chorioamnionitis are ascending cervicovaginal bacteria (Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis, Bacteroides, group B Streptococcus and E. coli); transplacental transmission during maternal bacteremia (e.g. Listeria monocytogenes) which are rare; prolonged labor; premature rupture of membranes (PROM); pathological bacterial colonization of vaginal tract (e.g., sexually transmitted diseases (STD), urinary tract infections); iatrogenic, such as multiple digital vaginal exams, amniocentesis and chorionic villous sampling are some of the known risk factors for chorioamnionitis (19,63).

Several strategies can be implemented in order to lower stillbirth. Good antenatal care packages should include regular appointments-consultations, ultrasounds, screening for fetal growth restriction and pregnancy risks and monitoring baby movement through kick counting, especially in the third trimester (19,64). Likewise, the education of pregnant women and their families should be a high priority.

The paper by Robert L Goldenberg *et al.* called "Stillbirths: the vision for 2020" was published in 2011, it adresses goals to accomplish before the year 2020 (65). These goals can be summarized as following. By 2020 high-income countries shall reduce third-trimester stillbirth rates to less than 5 per 1000 births and eliminate all preventable stillbirths. Whereas in low-income and middle-income countries, the goal is to reduce stillbirth by a minimum of 50%.

Furthermore, Jerzy Stanek described the hypoxic patterns of placental injury from a pathologist perspective (66). He concluded that the placenta is not just showing one single sign of hypoxia and that microscopic signs of hypoxia should always be viewed along with the clinical context. He stated that placental maturation is the most discriminative and by far the most important feature to assess in the diagnosis of chronic in-utero hypoxia, but it is also the most difficult to assess and the least-reproducible placental feature, even by experienced placental pathologists (67). The later highlights the importance of good communication between pathologists and clinicians.

A limitation of our study was the fact that not all stillbirths underwent autopsy due to their parents wish. This is one of the reasons what makes counting and understanding the true nature of stillbirth difficult. Yet another limiting factor is that clinicians did not always send the placentas for pathological analysis. Furthermore the unpredictable count of deliveries happening outside of the hospital (e.g. at home) are masking the true epidemiology of stillbirth.

6. CONCLUSION

Our study confirms that pathological investigations, including fetal autopsy and placental examination, are contributing to far more understanding of the causes of stillbirth compared to the clinical diagnosis alone. This means that stillbirth cases, like any other perinatal death case, should never be left unseen by a trained pathologist in order to help to understand the causes of stillbirths on a global scale via classification system like ReCoDe to protect future pregnancies. So that pregnancies at the local hospitals will benefit from these information but even subsequent pregnancies of the affected women can be monitored more closely or genetic counseling can be advised in case of an inherited disease which lead to the stillbirth.

In this regard it is also paramound to emphasize the communication between the clinicians, most commonly obstetricians, and the pathologist. We can maximize the efficiency of an accurate diagnosis only if all involved parties communicate in a clear, objective and comprehensive manner. This applies not only when it comes to stillbirths or perinatal deaths but at any time when clinicians and pathologists communicate in favor of the patients health.

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8. SUMMARY

Objectives: to determine causes of stillbirth according to ReCoDe classification system, with emphasis on stillbirth cases classified only as "*mors fetus*" by clinicians.

Materials and methods: retrospective study over a time span of 7 years evaluated 115 stillbirths. The collected data included pathological data, both autopsy reports and placental pathological reports and clinical information from the autopsy request forms. All of the stillbirth cases were allocated into one of the ReCoDe category and subgroups. Autopsy findings were summarized into seven categories (Signs of hypoxia, Infection, Malformations, Maceration, Umbilical cord, Signs of hydrops and Rh iso-immunization) and each stillbirth case was allocated into one, the most significant category. Finally the clinical information were summarized into ten categories (Mors fetus, Prematurity + Mors fetus, Malformations, Placenta abruption, Infection, Rhesus (Rh) - isoimmunization, Hydrops, Umbilical cord strangulation or knot, Maternal disease, Twin pregnancy) and each stillbirth was allocated into one category.

Results: 60% of stillbirths were males, 73% were classified as late stillbirth (≥28th w.g.) and 77.4% of all cases were preterm babies (<37th w.g.).

The most common ReCoDe category was amniotic fluid (23.5%), all of the cases recorded were chorioamnionitis. Within the "Fetus" group of ReCoDe category, congenital anomalies were most prevalent (60.9%). "Preterm baby" was the most common clinical information (39.1%), while "Signs of hypoxia" was the most common autopsy finding (36.5%). The second most common clinical information was "*mors fetus*" (19.1%). We could allocate all cases of "*mors fetus*" in one of the autopsy categories, where "Signs of hypoxia" was the most common one (63.6%). Furthermore, preterm stillbirth was most often categorized within the ReCoDe "Amniotic fluid" group (28.1%) while term stillbirths were most often categorized within the ReCoDe group "Umbilical cord" and "Unclassified" (30.8% and 30.8%, respectively).

Conclusion: Pathological investigations are contributing to far more understanding of the causes of stillbirth compared to the clinical diagnosis alone and a proper communication between the clinican and pathologist is cruicial for detailed and accurate diagnosis.

9. CROATIAN SUMMARY

Naslov: Klasifikacija mrtvorođenčadi u KBC Split prema ReCoDe sustavu klasifikacije.

Ciljevi: Odrediti uzroke smrti kod mrtvorođene djece prema ReCoDe klasifikacijskom sustavu, s naglaskom na mrtvorođenčad s uputnom dijagnozom *mors fetus* kao jedinim kliničkim podatkom.

Materijal i metode: retrospektivno istraživanje obuhvatilo je 115 slučajeva mrtvorođene djece u u vremenskom razdoblju od 7 godina. Analizirani su obdukcijski zapisnici, patohistološki nalazi posteljica te klinički podatci koji su preuzeti iz zahtjeva za obdukciju. Svi slučajevi su klasificirani prema ReCoDe klasifikacijskom sustavu.
Patološke dijagnoze proizašle iz obdukcijskih zapisnika podjeljene su u sedam kategorija (znakovi hipoksije, infekcija, malformacije, maceracija, pupčan vrpca, znakovi hidropsa, Rh-iso-imunizacija), a klinički podatci u deset kategorija (mors fetus, prematurus+mors fetus, malformacije, abrupcija posteljice, infekcija, Rh-isoimunizacija, hidrops, strangulacija pupčanom, vrpcom ili pravi čvor pupčane vrpce, bolesti majke i blizanačke trudnoće), svakom slučaju je dodjeljena jedan od navedenih kategorija patoloških dijagnoza i kliničkih podataka.

Rezultati: 60% mrtvorođenčadi je bilo muškog spola, 73% slučaja spada u kasnu mrtvorođenost (≥28tj. gestacije) , a 77,4% slučajeva su prematurusi (<37tj. gestacije).
Najučestalija ReCoDe kategorija je bila amnionska tekućina (23,5%) a svi zabilježeni slučajevi te kategorije su korioamnionitisi. Kongenitalne anomalije su najučestalija ReCoDe podgrupa u kategoriji "Fetus" (60,9%). Najučestaliji klinički podatak je bio "Prematurus" (39,1%) , a "Znaci hipoksije" najčešći patološki nalaz obdukcije (36,5%). Drugi po učestalosti klinički podatak je bio "*mors fetus*" (19,1%), a u toj skupini je najčesći patološki nalaz bio "Znaci hipoksije" (63,6%). "Amnionska tekućina" je bila najčešća ReCoDe grupa u skupini prematurusa (28,1%) dok je uzrok smrti terminske mrtvorođenčadi najčešće klasificirana u ReCoDe grupe "Pupčana vrpca" i "Neklasificirano" (30,8% i 30,8%).

Zaključci: Obdukcija i patohistološka analiza ploda i posteljice od iznimne su važnosti u utvrđivanju uzroka smrti mrtvorođene djece, pri čemu ključnu ulogu ima dobra komunikacija i međusobna suradnja patologa i kliničara.

10. CURRICULUM VITAE