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Review Article

The Incidence of HELLP Syndrome as a Complication of Preeclampsia and As a Determining Factor of Premature Birth

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Abstract

Introduction: HELLP syndrome is a variant of preeclampsia that evolves with hemolysis, elevated transaminases and bilirubin as well as thrombocytopenia, being able to generate severe complications during gestation.

Objective and Methodology: We did a retrospective study over a period of 6 years (2013-2018) on incidence, timing and complications generated by HELLP syndrome. At a total of 14,883 births, we reported 12 cases of HELLP syndrome representing 0.08%. At the same time it represents 5.06% of preeclampsia cases and 1.36% of the total pregnancies that have evolved with pregnancy-induced hypertension. At a number of 877 tasks that evolved with the HTA induced by pregnancy, preeclampsia cases were in the number of 238 (27.13%), and those with HELLP syndrome in the number of 12 (1.36%).

Results: All 12 cases OF HELLP syndrome were born prematurely by disrupting the course of pregnancy through the predominantly performed Caesarean section, in the percentage of 75% in maternal interest and 25% in the fetal interest resulting only in grade III and IV premature who died 2, both antepartum.

Conclusions: Hepatic impairment by cytolysis, secondary anemia, thrombocytopenia, cause the syndrome to be the determining factor of premature birth and chronic fetal suffering.

INTRODUCTION

One of the high blood pressure (HBP) induced complications of pregnancy is also the HELLP syndrome. It was first observed in 1954 by Pritchard [1-3] and is defined by Weinstein as the association of 3 biological disorders with preeclampsia [4-7]:

1. Hemolysis H

2. levated Liver enzymes EL

3. Low Platelets LP

Over time, each of these symptoms underwent changes in fracture limits, with the exception of thrombocytopenia whose diagnostic value remained constant, ie the platelet count was below 100,000 / ml [8] (Table 1).

Although some authors consider HELLP syndrome to be a simple syndrome, its association with preeclampsia makes us consider it a complication of pregnancy-induced hypertension, although mortality up to 24% is not always related to the syndrome but rather preeclampsia [4,5].

The name of the syndrome results from the acronym of the main HELLP symptoms. Mac Kaena rated the frequency in 12% of cases of eclampsia [9] compared to other authors who considered an incidence of 10-14% in preeclampsia patients and 30% in those with eclampsia. It is also estimated that in 69% of cases, the syndrome occurs antepartum and 30% postpartum in the early hours [6,10].

At present, it is estimated that within the syndrome thrombocytopenia is below 100,000 / ml [11], hemolytic anemia characterized by the presence of schizocytes in peripheral blood smear, decreased haptoglobin, bilirubin binding greater than 12 mg / l and lactate hydrogenease (LDH) values above 600 U / l and cytolysis characterized by increased transaminases (GOT and GPT) greater than 70 U / l [12-14,6,2,3,15].

Table 1: Representing the studied lot according to incidence of HELLP syndrome, preeclampsia and pregnancy-induced HTA-induced pregnancies.

YEAR	TOTAL BIRTHS	PIH		PREECLAMPSIA		HELLP SYNDROME		PREMATURE BIRTHS	
		Nv	%	Nv	%	Nv	%	Nv	%
2013	2148	133	6.08	36	1.64	2	0.09	254	11.63
2014	2354	133	5.64	61	2.59	2	0.08	251	10.66
2015	2517	102	4.05	31	1.23	2	0.07	321	12.75
2016	2564	79	3.08	34	1.32	2	0.07	300	11.70
2017	2608	71	2.72	42	1.61	3	0.11	227	8.70
2018	2656	109	4.10	34	1.28	1	0.03	278	10.46
TOTAL	14883	627	4.21	238	1.59	12	0.08	1631	10.95

Perinatal mortality varies between 7.7 and 60%, fetal intrauterine death being estimated at 19.3%, fetal mortality not related to common syndrome [16,17].

HELLP syndrome may be associated with an increased risk of abruption of normal inserted placenta [18,10], hepatic subcapsular hematoma, renal failure [16,19,15], pulmonary edema, CID [4,13,20,21], AVC, premature birth [22,23] fetal death in utero and maternal death [24].

There is a risk of post-operative bleeding and tendency to form wound hematomas, especially abdominal, in these pregnant women.

Clinical symptoms are nonspecific, consisting of:

- Epigastric papules

- Dyspeptic phenomena

- Pseudogripal phenomenon

Sometimes elevated blood pressure (BP) may be missing from the clinical picture [10,16,8]. Pregnancy with HELLP syndrome will be treated as a pregnant woman with severe preeclampsia, a particular focus being on treating coagulation problems [25,26].

Management of HELLP syndrome treatment should assess the preferred birth-time decision point to over 34 weeks of gestation [22,25,27]. Prior to 34 weeks of gestation, it may be tempting to go through this gestational age to receive a steroid cure for lung maturation and prophylaxis of respiratory distress syndrome [26,24]. This is done through strict echographic, cardiotocographic and blood pressure monitoring.

MATERIALS AND METHODS

At the base of the HELLP syndrome, there is preeclampsia, which at its origin has acute hypertension occurring in the last trimester of pregnancy, with the exception of glomerulonephrites [10,16]. Sibai was the one who resumed the initial criteria he had completed [2,3]. In the cytopathogenicity of preeclampsia there are a number of placental changes that generate placental ischemia [4,5,18,17,19,21,29,30,15].

We conducted a 6-year retrospective study (2013-2018) looking at maternal-fetal incidence, treatment, progression and prognosis in these particularly serious cases with regard to the HELLP syndrome.

In a total of 14,883 births that occurred during the 6 years studied, 12 cases of HELLP syndrome were reported, representing 0.08%. At the same time, this represents 5.06% of cases of preeclampsia and 1.36% of all pregnancies that have evolved with pregnancy-induced HBP. The incidence of all pregnancies evolved with pregnancy-induced HBP, including preeclampsia and HELLP syndrome, was 877 cases, representing 5.89%. Of these, preeclampsia cases were 238 (27.13%), and those with HELLP syndrome 12 (1.36%) .

The 12 cases of HELLP syndrome occurred in 5 cases (41.66%), in 4 cases (33.33%) secondary and in 3 cases (25%) in multiple gaps. At the same time after parity in 6 (50%) cases occurred in primipara, in 5 (41.66%) secundipara and in one case (8.33%) multipara (Table 1-3), showing the group studied after gestation.

After the residence area, 9 cases (75%) were from the urban area and 3 (28%) from the rural area. From the total number of cases that evolved with HELLP syndrome, one (8.33%) was a twin pregnancy. Thus, from the pregnancies that developed HELLP syndrome, 13 newborns resulted, 12 of which had a weight of less than 2500 g, all premature, of which in 6 (50%), the birth weight was between 500-1000 g, and in 6 (50%) of cases the birth weight was between 1001-1500 g, hence the HELLP syndrome is involved as the decisive factor in the premature birth etiology, all 12 cases having premature birth, of which they have premature third and fourth grade results. All of these births were resolved by cesarean section performed in maternal and fetal interest. Of the newborns resulting from these pregnancies, two girls died, one (8.33%) being born dead and one (8.33%) with Apgar 2 at birth. We mention that there were 168 premature births from pregnancies that evolved with PIH, preeclampsia and HELLP syndrome, accounting for 19.15% of them (Table 4-7).

After the age of pregnant women who developed HELLP syndrome, I found that 91.65% were under the age of 30 and only

Table 2: Representing the Studied Lot According To Gestation

GI		GII		MULTIGESTA		TOTAL	
Nv	%	Nv	%	Nv	%	Nv	%
5	41.66	4	33.33	3	25	12	99.99

Table 3: Representing the Studied Lot According To Parity

PI		PII		MULTIPARA		TOTAL	
Nv	%	Nv	%	Nv	%	Nv	%
6	50	5	41.66	1	8.33	12	99.99

Table 4: presenting the distribution of premature births to evolved cases that evolved with PIH, preeclampsia HELLP Syndrome.

ANUL	PARAMETER	FETAL WEIGHT									
		gr.IV prematurity		gr. III prematurity		gr.II prematurity		gr.I prematurity			
		500-1000		1001-1500		1501-2000		2001-2500		TOTAL	
		Vn	%	Vn	%	Vn	%	Vn	%	Vn	%
2013	PIH	1	8.33	2	13.33	3	11.53	6	12	12	11.65
	PREECLAMPSIA	2	11.76	4	23.52	4	28.57	3	17.64	13	20
	HELLP	1	8.33	1	8.33	-	-	-	-	2	16.66
2014	PIH	2	16.66	4	26.66	4	15.38	7	14	17	16.50
	PREECLAMPSIA	2	11.76	3	17.64	3	21.42	3	17.64	11	17.74
	HELLP	-	-	2	16.66	-	-	-	-	2	16.66
2015	PIH	3	25	2	13.33	3	11.53	8	16	16	15.53
	PREECLAMPSIA	4	23.52	4	23.52	3	21.42	4	23.52	15	23.07
	HELLP	1	8.33	4	33.33	-	-	-	-	5	41.66
2016	PIH	3	25	1	6.66	4	15.38	11	22	19	18.44
	PREECLAMPSIA	3	17.64	3	17.64	2	14.28	4	23.52	12	18.46
	HELLP	1	8.33	1	8.33	-	-	-	-	2	16.66
2017	PIH	1	8.33	1	13.33	5	19.23	8	16	15	15.53
	PREECLAMPSIA	3	17.64	1	5.88	1	7.14	1	5.88	6	9.23
	HELLP	2	16.66	1	8.33	-	-	-	-	3	50
2018	PIH	2	16.66	4	26.66	7	26.92	10	20	23	22.33
	PREECLAMPSIA	3	17.64	2	11.76	1	7.14	2	11.76	8	12.30
	HELLP	1	8.33	-	-	-	-	-	-	1	12.5
TOTAL	PIH	12	41.77	14	46.87	26	65	50	74.62	102	61.30
	PREECLAMPSIA	17	58.62	17	53.12	14	35	17	25.37	65	38.69
	HELLP	6	35.29	9	35.29	-	-	-	-	15	18.46
		35	17.29	40	19.04	40	23.80	67	39.88	182	99.99

Table 5: Presenting the Premature Births Associated With PIH

YEAR	TOTAL BIRTHS	PIH		PREECLAMPSIA		HELLP SYNDROME		PREMATURE BIRTHS		PREMATURE BIRTHS ASOCIATED WITH PIH	
		Vn	%	Vn	%	Vn	%	Vn	%	Vn	%
2013	2.148	133	6.08	36	1.64	2	0.09	254	11.63	27	15.78
2014	2.354	133	5.64	61	2.59	2	0.08	251	10.66	30	15.30
2015	2.517	102	4.05	31	1.23	2	0.07	321	12.75	33	16.92
2016	2.564	79	3.08	34	1.32	2	0.07	300	11.70	33	28.69
2017	2.608	71	2.72	42	1.61	3	0.11	227	8.70	25	21.65
2018	2.656	109	4.10	34	1.28	1	0.03	278	10.46	32	22.22
TOTAL	14.883	627	4.21	238	1.59	12	0.08	1631	10.95	182	20.75

Table 6: Presenting the Studied Lot According To Age

27 yo		28 yo		29 yo		30 yo		35 yo		Total	
Vn	%	Vn	%	Vn	%	Vn	%	Vn	%	Vn	%
3	25	4	33.33	2	16.66	2	16.66	1	8.33	12	99.98

Table 7: Presenting the Studied Lot According To The Apgar Score Associated With Hellp Syndrome

27 WEEKS		28 WEEKS		29 WEEKS		30 WEEKS		35 WEEKS		Total	
Vn	%	Vn	%	Vn	%	Vn	%	Vn	%	Vn	%
3	25	4	33.33	2	16.66	2	16.66	1	8.33	12	99.98

Table 8: Representing the Studied Lot According To the Gender of the Newborns Resulted From Pregnancies Complicated With Hellp Syndrome

Male		Female		TOTAL	
Vn	%	Vn	%	Vn	%
8	66.66	4	33.33	12	99.96

Table 9: Representing the Studied Lot According To platelet Count

20,000-40,000		50,000-60,000		60,000-80,000		TOTAL	
Vn	%	Vn	%	Vn	%	Vn	%
5	41.66	4	33.33	3	25	12	99.99

Table 10: representing the studied lot according to transaminase value

50-100ui		100-500ui		500-700ui		TOTAL	
Vn	%	Vn	%	Vn	%	Vn	%
3	25	5	41.66	4	33.33	12	99.99

Tabel 11: Representing the Evolution of Hepatic Parameters during Pregnancy [30]

INCREASED FACTORS	CONSTANT FACTORS	INCREASED FACTORS
-alkaline phosphatase -coagulation factors II, VII, VIII, X -fibrinogen -transferrin -alfpafetoprotein	-aspartateaminotransferase (AST) -alaninaminotransferase (ALAT) -bilirubin -gamaglutamil transpeptidase (GGT) -glutamatdehydrogenase GLDH	-proteinemy -gamaglobulin in particular IgG -albumin -iron

one case (8.33%) was 35 years. The mean age of the studied lot was 28 years 8 months 3 days.

After gestational age 7 (78.33%) had gestational age below 28 weeks, 4 (33.32%) with 29-30 weeks and 1 case (8.33%) 35 weeks (Graph 1-6).

After the prematurity of newborns resulting from pregnancies that evolved with PIH, preeclampsia and HELLP syndrome, the situation was the following (Table 8-10):

-prematurity gr.I 2001-2500g 67 cases (39.88%)

-Prematurity gr.II 1501-2000g 40 cases (23.80%)

-Prematurity gr.III 1001-1500g 30 cases (19.04%)

-Prematurity gr.VI 500-1000g 29 cases (17.26%)

Total 168 cases (99.98%)

Out of the total of 1631 premature births, representing a 10.95% prematurity, 877 (53.77%) were premature births resulting from pregnancies that evolved with PIH regardless of form.

According to APGAR score at birth, 10 (83.33%) newborns had APGAR 0-6 and only 2 (16.66%) cases had an APGAR score of 7-8. This proves an advanced degree of the antepartum fetal suffering of these girls.

Without any special significance, we mention that 8 (66.66%) were male and 4 (33.33%) female.

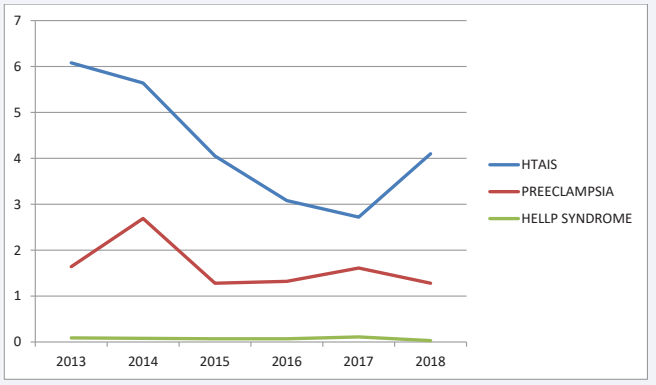
HELLP syndrome is a clinical but especially laboratory syndrome that complicates about 20% of cases of severe preeclampsia [15] on our lot of 5.06%. From this point of view, 5 (41.66%) of the cases presented thrombocytopenia with a platelet count of 20,000-50,000, in 4 (33.33%) with a value between 50,000-60,000 / mm3 and in 3 cases (25%) with a value between 60,000 to 80,000 / mm3.

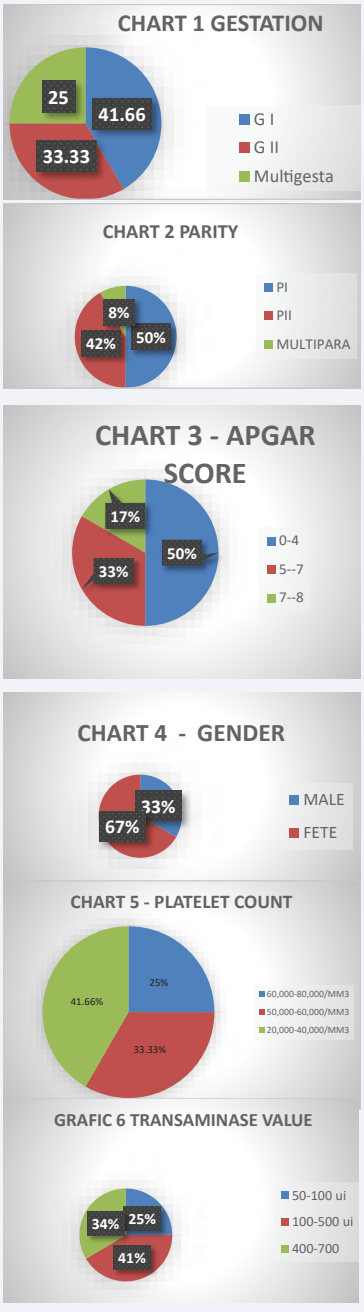
Even if the value of the transaminases oscillated, they were increased, sometimes even exaggerated, with 74.99% having values above 100 (Table 11,12).

Proteinuria had elevated levels between 3-5 g and a total proteinemia generally lower between 4.5-6 g%. Also in all cases we found a decrease in fibrinogen below 100 mg / ml.

Tabel 12: Representing the Evolution of Other Factors during Pregnancies Associated With Hellp Syndrome

INCREASED FACTORS	CONSTANT FACTORS	DECREASED FACTORS
-alkalin phosphatase -transferin -bilirubin -transaminasesASTandALT -coagulation factors VII, VIII and X -proteinuria	-alfhafetoprotein -gamaglutamiltranspeptidase	-proteinemy -albumins -iron -gamaglobulin ig G -hematocrit -hemoglobin
-LDH>twice the upper limit of GLDH -Glutamatlactodehidrogenase	-	-





Graphs 1-6

The clinical symptoms encountered by us on the studied group were as follows:

- Epigastria pain commonly found in all cases

-dyspeptic simptoms in 75% of cases

- Pseudogripal phenomenon - we did not notice our lot

- Increased values of arterial tension can be missed sometimes, but we have not met any cases in the lot we studied

From a clinical point of view, arterial blood tension values were increased with diastolic TA at least 110 mmHg and maximum 180-200 mmHg rebels to treatment. Symptomatically, pregnant women accused of headache, epigastralgia, pain in the right hippocampus, icteric coloration of sclera and tegument, anorexiaand fatigue.

The phenomena disappeared with the interruption of pregnancy, which reveals the role of placenta in the etiopathogenesis of the syndrome [21,28,29,15].

HELLP syndrome can cause a number of complications, even the risk of postoperative bleeding occurring in a disseminated intravascular coagulation syndrome or afibrinogenemia. In assessing changes in some parameters during HELLP syndrome, we must also keep in mind the physiological changes of some liver parameters that occur during pregnancy [30].

In comparison with these parameters, the following changes are observed in HELLP syndrome:

The perinatal mortality of newborns resulting from pregnancies that evolved with HELLP syndrome was 2 cases, representing 16.66% of all fetal deaths, of which one case (8.33%) occurred antepartum. This, along with the APGAR index at birth, proves the involvement of the syndrome in the occurrence of fetal distress.

CONCLUSIONS

1. HELLP syndrome is a variant of preeclampsia with fetal distress, haemolysis, elevated transaminase and bilirubin levels, and a decrease in thrombocytes in luckily being rare

2. The incidence of HELLP syndrome on the group we studied was 0.08% of all pregnancies and in 1.36% of pregnancies that evolved with PIH

3. Currently the role of placenta is well defined in the etiopathogenesis of the syndrome, the placental ischemia phenomena having a determinant role

4. HELLP Syndrome is a determinant of premature birth in all cases studied by us resulting in premature newborns of Grade III and IV

5. Hepatic impairment, by cytolysis, secondary anemia and thrombocytopenia make the syndrome a determinant of premature birth and fetal suffering

6. Coagulation disorders caused by severe thrombocytopenia and decreased fibrinogen value are the basis for the occurrence of disseminated intravascular coagulation syndrome which may worsen both maternal and fetal prognosis

7. In preterm newborns of third and fourth grade in our group resulting from pregnancies that evolved with HELLP syndrome, the mortality was 2 cases (16.66%) of which a death was anepartum

8. The incidence of premature birth in pregnancies that evolved with HTAIS is double compared with the pregnancies that evolved without HTAIS that means 20.75% versus 10.95

REFERENCES

1. Pritchard JA, MacDonald PC, Gant MF. Williams Obstetrics Ed. 17; Norwalk, Appletone Contane Croft. 1985.
2. Sibai BM, Watson DL, Will GA, Spinnato JH, Anderson GD. Maternal-fetal correlations in patients with severe preeclampsia-eclampsia. Obstet-Gynecol. 1983; 62: 745-750.
3. Sibai BM. The HELLP Syndrome (hemolysis, elevated liver enzymes and low platelets count): Much and about nothing? Am J Obstet Gynecol. 1990; 162: 311-316.
4. Munteanu I. Tratat de obstetrica Buc, Ed. Academiei Vol. II 2006.
5. Hrubaru N, Muntenu I. Hipertensiunea arteriala indusa de sarcina. Timisoara, Ed. Mirton, 1999; 71-74.
6. Gatje R, Eberle C, Scholze C, Lubke M, Solbach C, Muschel K, et al. All. Kurzlehrbuch, Gynakologie und Geburtshilfe. Ed. Thieme, Vereag-Stuttgard- New York. 2015; 392-393.
7. Weinstein L. Syndrome of hemolysis elevated liver enzymes and low platelets count: severe consequence of hypertension in pregnancy. Am J Obstet Gynec. 1982; 142: 159-167.
8. Peltecu Gheorghe. Obstetrica Ginecologie in: Tratat de chirurgie, Buc. Ed. Academiei Rom. 2014; 608-611.
9. Mac Keene J, Dover ML, Brame RG. Preeclampsia associated with hemolysis, elevated liver enzymes and low platels-An Obstetric. Emergency? Obstet Gynec. 1983; 62: 751-754.
10. Goerke KJ, Steller A. Valet-Klinikleitfaden Gynacologie Geburtshilfe; Ed. Elsevier 2015; 161-174.
11. Burrows RF. Thrombocytopenia in the Hypertension disorders of pregnancy; Clin Exper Hipert 1990; B9: 109-210.
12. Barten JR, Riely CA, Adamec TA, Shanklin DR, Khoury AD, Siboi BM. Hepatic histopatologic condition does not correlatewith laboratory abdormalities in HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Am J Obstet Gynecol. 1992; 167: 1538-1543.
13. Burrows RF. Thrombocitopenia in the hypertension disorders of pregnancy. Clinic Expert Hypert. 1990; B 9: 199-210.
14. Vidaeff AC, Bares VA. Hepatic involvement in Preeclampsia in: Maternal- Fetal risk in Gestezis. Ed. Cic Editione Internationala Roma. 1996; 93-112.
15. Teodorescu M, Georgescu L, Tudose M. Patologia placentei, Timisoara Ed. Facla; 1977; 113-120.
16. Gluhovschi A,Trandafirescu V, Schiller A, Petrica C. Rinichiul si hipertensiunea arteriala; Ed. Helicon Timisoara 1996; 279-308.
17. Hrubaru M,Tudose M, Suflea P, Hrubaru B, Romosan I. Modificari

placentare in preeclampsie-al XI-lea Cong. Nat. Obstet.-Ginec. Timisoara. 1999; 254-255.

18. Brosens I, Renaer M. On the pathogenesis of placental infarcts in preeclampsia. J Obstet.Gynec Br Commonw. 1972; 79: 794-799.

19. kumar D. Chronic placental ischemia in relation to toxemia of pregnancy. A preliminary raport. Am J Obstet Gynec. 1962; 84: 1323-1329.

20. Martin JM, Stedman CM. Imitators of preeclampsia and HELLP Syndrome. Obstet Gynecol Clin North Am. 1991; 18: 181-198.

21. Anastasiu Popov Diana Maria, Cean A, Boju MF, Adrian Gluhovschi, Panoitescu Carmen, Paunescu Virgil, et al. Explants Isolated Human Planceta and ombilical cord cellls share characteristics of Both epithelial and mesenchimal stem cells. Rom J Morphol. Embryol. 2016; 57:382-390.

22. Martin JM, Persy KG, Miles JF, Blake PC, Magann EF, Roberts WE, et al. The interrelationship of eclampsia, HELLP Syndrome and prematurity: Cofactors for significant maternal and perinatal risk. Br J Obstet Gynecol. 1993; 100: 1095-1100.

23. Munteanu I, Rippmann ET, Hrubaru N. Maternal-fetal risks in gestosis. CIC Edizioni Internazionali, Rome, 1996.

24. Anastasiu MD, Cean A, Bojin F, Gavriliuc O, Gluhovschi A, Anastasiu D, et al. Fiziologia-Physiology 2015; 25.1: 26-30-Categoria B+ CNCSIS

25. Bameanu G, Dumitru G, Steriade C, Dragomirescu R. Medical management of gestational hypertension-Maternal-fetal risk in Gestosis. CIC Edizioni Internazionali. 1996; 3-7.

26. Anastasiu MD, Cernat L, Cristea M, Bojin F, Gavriliuc O, Gluhovschi A, et al. In Vitro Assessment of Tumor-Associated Fibroblasts' Proliferation Ability and Viability. Fiziologia-Physiology 2015; 25.3: 10-15-Categoria B+ CNCSIS

27. Diana Anastasiu, Florina Bojin, Gluhovschi A, Sevillia Balu, Anda Vizitiu, T. Bold, Craina M, Paunescu V- Stem Cells and the Placental Stem Cells Rev. Fiziologia 2013 23.2 (78) pag. 4-10 – Categoria B+ CNCSIS

28. Munteanu I. Structural modification of the placenta in preeclampsia in: "Increasingly safe and successful pregnancies". Ed. Elsevier. 1996; 65-68.

29. Rippmann ET. The signifiance of EPH Gestosis-vol. 22 nd; International Comp. on Pathophysiology of pregnancy. Budapest. Book of advanced abstract 1990; 136-141.

30. Alvarez H, Morel RL, Benedetti UL, Scanarelli M. Trophoblast hyperplasia and maternal arterial preasure at term. Am J Obstet Gynec. 1969; 105: 1015-1021.