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Original article

Analysis of relation between placental lesions and perinatal outcome according to Amsterdam criteria: a comparative study

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Summary. *Background:* To verify the correlation between histological examination of the placenta (HP), classifying the lesions according to the Amsterdam criteria (AC), and the main neonatal pathological patterns. *Methods:* This prospective study carried out at the University of Bari between May 2015 and May 2017,enrolled 350 pregnant women. Complete obstetric history and HP was collected. 380 newborns were also enrolled. The analysis was also carried out by comparing the incidence of the various placental pathologies in the sample of physiological pregnancies (PP), represented by 142 cases, with the incidence of the group with placental anomalies (PA). The statistical software used was STATA MP11. *Results:* Respiratory disorders (61 cases) are significantly correlated with generic PA (p=0.006). Neonatal sepsis (15 cases) was significantly correlated with placental inflammation (p=0.035) and villitis of unknown origin (p=0.039).Twin pregnancies (50 cases) were correlated with generic PA (p=0.00001) and late maternal malperfusion (p=0.00001). Congenital cardiopathies (50 cases) were correlated with the villitis of unknown origin and PA (p=0.0000). Preterm birth (145 cases)was correlated with the premature malperfusion (p=0, 0011) and PA (p=0.0000); SGA (low weight in relation to the gestational age - 75 cases) neonates were correlated with the early malperfusion (p=0.00000) and the generic PA (p=0.00000). *Conclusions:* The present study has therefore verified whether in reality the HP can be of great help to the neonatologist in the nosological and therapeutic setting of the pathological newborn. The pathological examination of the placenta is nevertheless essential to clarify the causes of the stillbirths and that these causes are particularly important for the obstetric and neonatal outcome of subsequent pregnancies. (www.actabiomedica.it)

Key words: placenta, Amsterdam criteria, istological exam, placental disfunction, placental lesion

Introduction

The aim of the study is to verify the correlation between HP, classifying the lesions according to the AC, and the main neonatal pathological patterns (prematurity and low birth weight, malformations, infectious, metabolic, respiratory pathology, maternal diabetes). Placental dysfunction as a cause of stillbirth has increasingly become a focus of research effort with recognition that placental disorders are the cause of death in up to 65% of stillbirths. Much work remains to disseminate the new information to the pathologists and clinicians. Placental diseases can be very useful in a wide variety of ways, including the immediate diagno-

sis of important conditions affecting both the mother and the newborn, identifying conditions that could occur in subsequent pregnancies, separating the clinical syndromes into distinct phenotypes for future investigations, and discovering the hidden causes of unexpected adverse outcomes (1, 2). A sub-optimal performance of the placental function can result in morbidity and even maternal and fetal mortality. Therefore, there are some indicators that placental lesions (PL) are the main risk factors for fetal death (3).

HP available in short time should be helpful for a correct and timely diagnosis of neonatal pathological conditions or to shorten the diagnostic procedures in cases of delayed event.

Material and methods

This prospective study carried out at the University of Bari between May 2015 and May 2017,enrolled 350 pregnant women. Complete obstetric history and HP was collected. 380 newborns were also enrolled. Their conditions were known at birth and neonatal pathologies until the first month of life were reported. All patients have signed informed consent. The present study was carried out in accordance with ethical standards. Both obstetricians and neonatologists have known the outcome of the HP only three months after birth.

350 placentas were analyzed according to the AC at the Pathological Anatomy of the Policlinico of Bari. After delivery, the placenta was carefully washed, weighed, examined in external appearance and placed with a buffer solution of formalin with a ph of 7.

All the placentas of high risk-pregnancies, with real or expected obstetric complications were collected. The placenta was analized on both the maternal and fetal sides; length and thickness of the umbilical cord were measured; researched the possible presence of ectasia, thrombi or real nodes. The chorionic-amniotic membranes were examined: once the breaking point was identified, a full-thickness section was prepared. The color and visibility of the eventual vascular insertion of the vessels was reported. After removal of the umbilical cord and membranes, the chorionic disk was examined on the fetal side to evaluate the status and distribution of the villi, then on the maternal side to identify the appearance of the cotyledons. Later, the chorion was sectioned to obtain parallel sections and to look for areas of necrosis, hemorrhage and infarction; also the functional areas have been sampled. These samples were dehydrated and included in paraffin. The histological sections were stained with hematoxylin-eosin and with Mallory's trichrome. PL considered, in accordance with the AC, are: early maternal malfunctioning, late maternal malpractice, fetal malperfusion, infection/placental inflammation, villitis of unknown origin, delay of maturation of the villi; placental alterations: generic term, which also includes those anomalies that have been excluded from the AC: intravenous hemorrhages and chorangiosis.

For each patient, the following information was taken into consideration: diagnosis of acceptance, IUGR, prom, gestational age, type of delivery, urine exam and vaginal culture, prophylaxis with cortisone, gestational hypertension.

After delivery, the neonates were followed during their admission to the Neonatology and Neonatal Intensive Care Department, taking into consideration: gestational age at birth, weight and classification at birth, malformative pathology, respiratory pathology, infectious pathology, metabolic pathology, exitus, apgar, phototherapy.

Statistical analysis was performed using the X2 test in order to verify the level of dependence between character distributions in two non-paired samples. A value of $p < 0.05$ was considered statistically significant. When necessary, the Yates correction was used for the continuity of the χ^2 test. The analysis was also carried out by comparing the incidence of the various placental pathologies in the sample of PP, represented by 142 cases , with the incidence of the group with placental anomalies. The statistical software used was STATA MP11.

Results

Our approach was considered crucial in order to clarify the different incidence of PL in pathological and PP. The different incidence of placental pathologies in the various forms of neonatal pathologies were analyzed (graph 1-7).

Graph 1-7.

Respiratory disorders (61 cases) are significantly correlated with generic PA (p=0.006); no correlation was evidenced with all the other alterations.

Neonatal sepsis (15 cases) was significantly correlated with placental inflammation (p=0.035) and villitis of unknown origin p=0.039); on the contrary,

it is not correlated with early and late maternal malperfusion, generic PA and the delay of development of the villi. SGA (low weight in relation to the gestational age - 75 cases) neonates were correlated with the early malperfusion (p = 0.00000) and the generic PA (p=0.00000); no relationship was found with the late maternal and fetal malperfusion, the villiti of unknown origin, the placental inflammations and the delay of the villi development.

Twin pregnancies (50 cases) were statistically correlated with generic PA (p=0.00001) and late maternal malperfusion (p=0.00001); no correlation was found with early maternal and fetal malperfusion, villitis of unknown origin, growth retardation of villus and placental inflammation.

Metabolic pathology (28 cases)was statistically correlated with premature maternal malfunction (p=0.0000), generic PA (p=0.0046) and maturation delay of the villi (pp=0, 00000); it is not correlated with late maternal malperfusion, the villiti of unknown origin, the fetal malperfusion, the placental inflammations.

Preterm birth **(**145 cases)was correlated with the premature maternal malperfusion (p=0, 0011) and PA (p=0.0000); on the other hand, it does not have a significant correlation with late maternal malfunctioning, fetal malperfusion, placental inflammation, retardation of villous development and villitis of unknown origin.

Congenital cardiopathies (50 cases) were statistically correlated with the villitis of unknown origin (p=0.00000) and PA (p=0.0000); no correlation was found with early and late maternal malfunctioning, fetal malperfusion, villi growth retardation and placental inflammations.

Neonatal exitus (7 cases) was recorded in a limited number of cases, so it is not possible to verify any difference in the incidence of placental pathologies, compared to the same lesions in the PP.

Discussion

The aim of this study is to verify the possibility of clinical use, diagnosis and treatment choice, in the Neonatology departments, of the results of the HP, classified according to the AC.

In the above analysis the different incidence of PL according to AC, found in newborns with the aforementioned pathologies, was compared to the same incidence of PL of PP.

This methodological approach was important in order to exclude the overlap of the incidence of PL between pathological and PP, a coincidence that would have rendered the HP virtually meaningless.

The results of the present study, on the other hand, showed significant differences in the incidence of the various placental pathologies, a consequence of the close correlation between neonatal pathology and previous PL.

We will therefore analyze the above differences below.

Early neonatal sepsis was significantly correlated with an increased incidence of placental inflammation and villitis of unknown origin. This data is in accordance with the studies by Yamada et al. which verified the highest incidence of neonatal pathological events (including sepsis) in association chorioamnionites (4, 5).

In our series, 15 cases of sepsis were identified, in which the association with the placental infections and with the histological villitis (p=0.0395) was highly significant. The significant correlation between SGA newborns and early maternal malperfusion, highlighted by HP, was evidenced.

The increased incidence of placental malperfusion in the SGA allows us to affirm that, in the neonatal judgment of the severity of the SGA are important as well as the cause of reduced birth weight (lack of perfusion or infection, chromosomopathy, etc.) even when this placental malfunctioning has established itself. Several studies, have evaluated the effect of vascular alteration of the placenta as a significant risk factor for the birth of SGA infants (6). The results therefore confirmed that the SGA is significantly correlated with the finding of early placental malfunctioning and with PA, according to the AC.

Although, the term SGA contains a series of pathophysiological conditions, in our series, the early placental malperfusion and the AC of PA were present in 75% of the SGA. This result could be very useful in the diagnosis and therapy, as it could direct the neonatologist towards a nosological framework, influencing the therapeutic choices.

Particular attention deserves the result of the placental study in preterm infants. Much of the recent literature, in fact, is almost unanimous in thinking that preterm birth is basically the result of an inflammation.

According to our study, the PL associated with preterm birth are early maternal malperfusion and generic placental alterations: early malperfusion is present in 26% versus 11% in PP (p=0.0011), while PA were present in 66% of preterm cases versus 40% of PP.

In conclusion, although premature delivery may be associated with placental infections as reported by Catov et al. and Guzick (2774 newborns with premature births, 32% chorioamnionitis versus 10% of PP), a fundamental role can be played by an early malperfusion, which could also be the consequence of previous coriamnionites, spontaneously resolved after therapy (7). The present data, represents an indication to a further analysis of the correlations between premature birth and PL.

Analysis of twins showed a significant increase in the incidence of late placental malfunction. The datum is revolutionary, underlining that the human placenta is not philologically suitable for supporting a twin pregnancy, throughout its duration.

In fact, 44% of twins have late placental malfunctions versus 16% of PP (p= 0.0001). It is not pleonastic to add that the late placental malperfusion is a unique picture of twin pregnancies.

This result is not in contradiction with the literature, according to which twin pregnancies have more PA. Our finding of increased incidence of late malperfusion confirms and better characterizes the generic data present in the literature. In fact, the correlation between generic PA and twin pregnancies, already supported by Eberle et al. and Weiner et al. , is expressed by an increased incidence of late perfusion, which we found in the placenta of the twins (8, 9).

Another strong point of our study concerns neonatal congenital malformations. The data of the literature have variously underlined the increased incidence of cord anomalies and of generic PL, of variations in the weight of the placenta, even if the topic data are lacking in literature. Matthiesen, in fact, has recognized the limit of study of the placenta in congenital heart disease.(10)

Therefore, compared to the literature, our study has brought new information such as the increased incidence of villiti of unknown origin (66% in the placenta of cardiopathies versus 19% of PP, p=0.000) and of PA (98% in cardiopathies against 2% of PP, p=0.00). Our data, therefore, are not in contradiction but complementary each other, as the weight of the placenta, the alterations of insertion of the funiculus, can be included in the "generic PA".(11)

Our study has added that, instead, the finding of villiti of unknown origin has an ezio-pathological meaning, as it is probably an early event in pregnancy,which determines the cardiopathy.

A weak point in our study is the lack of correlation between neonatal exitus and the considered PA, justified by the reduced number of died newborns (7 of 380). In recent years the role of the placenta in fetal deaths has however become increasingly clear: placental pathology is one of the main causes of fetal death and specifically the reduced perfusion is the main cause(12).

It can therefore be concluded that the pathological HP is nevertheless essential to clarify the causes of the stillbirths and that these causes are particularly important for the obstetric and neonatal outcome of subsequent pregnancies (12-16).

This concept was recently underlined by the provisions of the Ministry of Health which imposed the autopsy and HP in all cases of fetal death in utero (17).

The analysis of cases with perinatal asphyxia showed a significant increase in the incidence of PA (61% in neonatal asphyxia versus 23% of PP, p=0.06).

According to Roescher et al, the perinatal asphyxia is to be correlated with the disorders of the placental circulation, which is also confirmed by us. On the other hand, the correlation of perinatal asphyxia with placental inflammations, especially chorioamnionites, was not significant.

Our results therefore confirm that neonatal asphyxial events frequently have a possible PA as the main determinant, even if probably not exclusive. In fact, a diseased birth as it is known has different consequences from the point of view of the onset of hypoxia, which are based not only on the severity and duration of obstetric trauma, but also on the ability of the placenta to compensate for the reduction of the pH determined by the intrapartum trauma.

Conclusions

For years the study of placenta has fascinated various medical branches, looking for information useful to improve the perinatal prognosis. The absence of univocal classification of PL, the variability deriving from analysis influenced by subjectivity, the complexity of placental histology have made difficult any clinical relapse of the HP.

The advent of the AC has restored confidence to a clinical approach towards the HP.

This classification has many points that must be clarified, it has enabled scholars and now also to clinicians to start thinking about the HP as a tool to improve the neonatal prognosis. Particular interest in the HP begins to be present also by the neonatologists, but this interest is still slowed down due to the delay of the histological result, making its use impossible by the neonatologist. The present study has therefore verified whether in reality the HP can be of great help to the neonatologist in the nosological and therapeutic setting of the pathological newborn. The correlation analysis, implemented with rigor, has allowed us to provide preliminary data that can make concrete the clinical use of the neonatologist. In summary, we can sketch the following conclusions:

In the case of neonatal asphyxia, the attention of the neonatologist should not be concentrated only on intra-partum trauma but also on PA that make the newborn more sensitive to hypoxic stress.

In the case of neonatal sepsis, there is always a previous placental infection confirmed by the significant association with inflammatory infections or PL and with villitis of unknown origin. This can be used to anticipate the advent of the newborn's sepsis.

In SGA newborns the most determining factors are the early malperfusion (p=0.000) and the PA that represent 75% of the causes of preterms. This information in real time would allows to simplify the diagnostic approach, but above all, a prophylaxis of the subsequent pregnancy. Twin bigeminal pregnacy is not a pathological condition for the woman but a condition in which , the placenta is affected by the late malperfusion which, associated with PA, does not allow a physiological pregnancy.

The picture of PA present in gestational diabetes highlights long-lasting alterations (early malfunctions, especially delay of the maturation of the villi) that underline the need for an early correction of the metabolic syndrome. Considering that a large part of this series included women suffering from gestational diabetes, it follows that this type of diabetes should be diagnosed at the early stages of pregnancy, even if current diagnostic standards do not allow such diagnosis before 16-22 weeks. In this sense, the hope is that, it would be preferable to diagnose the dysmetabolism in the early stages of pregnancy. In premature birth it is not only to consider an infectious episode but also and above all early malperfusion, as well as the presence of PA. Much of these lesions intersect with the inflammatory lesions can be clarified only by a prospective multifactorial study. Finally, in the cardiac abnormalities, the villiti of unknown origin and the PA predominate, indicating the presence of intrinsic predisposing conditions that may have a proper marker in the PL .In conclusion, we still know very little about the placenta, but the journey has begun and will have to continue speaking a single language and above all using multifactorial analyzes, in the context of an event, the birth of a child). This analysis will undoubtedly contribute to the development of the artificial placenta, in a more or less near future.

Furthermore, our analysis could lay the foundations for a long-term study, to evaluate the growth of our own newborns and the physiological or pathological development of the same, also paying attention to the pathologies of development.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Khong TY, Mooney EE, Ariel I, et al. Sampling and Definitions of Placental Lesions: Amsterdam Placental Workshop Group Consensus Statement. Arch Pathol Lab Med 2016; 140(7): 698-713.
2. Annemiek M. Roescher, Albert Timmer, Jan Jaap H. M. Erwich, Arend F. Bos. Placental Pathology, Perinatal Death, Neonatal Outcome, and Neurological Development: A Systematic Review. PLoS One 2014; 9(2): e89419.

3. Korteweg FJ, Erwich JJ, Holm JP, et al. Diverse placental pathologies as the main causes of fetal death. Obstet Gynecol Obstet Gynecol 2009; 114(4): 809-17.
4. Yamada N, Sato Y, Moriguchi-Goto S, Yamashita A, Kodama Y, Sameshima H, Asada Y·Histological severity of fetal inflammation is useful in predicting neonatal outcome. Placenta 2015; 36(12): 1490-3.
5. Bae GE, Yoon N, Choi M, Hwang S, Hwang H, Kim JS. Acute Placental Villitis as Evidence of Fetal Sepsis: An Autopsy Case Report. Pediatr Dev Pathol 2016; 19(2): 165-8.
6. Becroft D.M.O. Thompson J.M.D. Mitchell. E.A. The epidemiology of placental infarction at. Placenta 2002; 23(4): 343-51.
7. Catov JM, Scifres CM, Caritis SN, Bertolet M, Larkin J, Parks WT. Neonatal outcomes following preterm birth classified according to placental features. Am J Obstet Gynecol 2017; 216(4): 411.e1-411.e14. doi: 10.1016/j.ajog.2016.12.022.
8. Eberle AM, Levesque D, Vintzileos AM, Egan JF, Tsapanos V. Placental pathology in discordant twins. Salafia CM. Am J Obstet Gynecol 1993; 169(4): 931-5.
9. Weiner E, Kahn M, Giltvedt K, et al. Nonpresenting Dichorionic Twins and Placental Vascular Malperfusion. Obstet Gynecol 2017; 129(6): 1109-1117.
10. Matthiesen NB, Henriksen TB, Agergaard P, et al. Congenital Heart Defects and Indices of Placental and Fetal Growth in a Nationwide Study of 924 422 Liveborn Infants. Circulation 2016; 134(20): 1546-1556.
11. Albalawi A, Brancusi F, Askin F, et al. Placental Characteristics of Fetuses With Congenital Heart Disease. J Ultrasound Med 2017; 36: 965-972.
12. Annemiek M. Roescher Placental Pathology, Perinatal Death, Neonatal Outcome, and Neurological Development: A Systematic Review. 2014 Plos One.
13. Incerpi MH, Miller DA, Samadi R, Settlage RH, Goodwin TM. Stillbirth evaluation: What tests are needed? Am J Obstet Gynecol 1998; 178(6): 1121-5.
14. Heazell AE, Martindale EA. Can post-mortem examination of the placenta help determine the cause of stillbirth? J Obstet Gynaecol 2009; 29: 225-228.
15. Kidron D, Bernheim J, Aviram R. Placental findings contributing to fetal death, a study of 120 stillbirths between 23 and 40 weeks gestation. Placenta 2009; 30: 700-704.
16. Korteweg FJ, Erwich JJ, Timmer A, et al. Evaluation of 1025 fetal deaths: Proposed diagnostic workup. Am J Obstet Gynecol 2012; 206: 53.e1-53.e12.
17. Raymond W. Redline, Classification of placental lesions. Am J Obstet Gynecol 2015; 213(4 Suppl): S21-8.

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