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Women with psychotic episodes during pregnancy show increased markers of placental damage with Tenney-Parker changes

Miguel A. Ortega[1,2], Oscar Fraile-Martinez[1,2], Cielo García-Montero[1,2], Sonia Rodriguez-Martín[1,3], Rosa M. Funes Moñux[1,3], Leonel Pekarek[1,2], Coral Bravo[4,5,6], Juan A. De Leon-Luis[4,5,6], Miguel A. Saez[1,2,7], Luis G. Guijarro[2,8], Guillermo Lahera[1,2,9], Jorge Monserrat[1,2], Roberto Rodriguez-Jimenez[10,11], Jose V. Saz[12], Julia Bujan[1,2], Natalio García-Honduvilla[1,2], Melchor Alvarez-Mon[1,2,13] and Miguel Angel Alvarez-Mon[1,2,14]

[1]Department of Medicine and Medical Specialities, Faculty of Medicine and Health Sciences, University of Alcalá, Alcalá de Henares, [2]Ramón y Cajal Institute of Sanitary Research (IRYCIS), Madrid, [3]Service of Pediatric, Hospital Universitario Principe de Asturias, Alcalá de Henares, [4]Department of Public and Maternal and Child Health, School of Medicine, Complutense University of Madrid, Madrid, [5]Department of Obstetrics and Gynecology, University Hospital Gregorio Marañón, [6]Health Research Institute Gregorio Marañón, Madrid, [7]Pathological Anatomy Service, Central University Hospital of Defence-UAH Madrid, [8]Unit of Biochemistry and Molecular Biology (CIBEREHD), Department of System Biology, University of Alcalá, [9]Psychiatry Service, Center for Biomedical Research in the Mental Health Network, University Hospital Príncipe de Asturias, Alcalá de Henares, [10]Department of Legal Medicine and Psychiatry, Complutense University, [11]Institute for Health Research 12 de Octubre Hospital, (Imas 12)/CIBERSAM (Biomedical Research Networking Centre in Mental Health), Madrid, [12]Department of Biomedicine and Biotechnology, Faculty of Medicine and Health Sciences, University of Alcalá, [13]Immune System Diseases-Rheumatology and Internal Medicine Service, University Hospital Príncipe de Asturias, CIBEREHD, Alcalá de Henares and [14]Department of Psychiatry and Mental Health, Hospital Universitario Infanta Leonor, Madrid, Spain

Summary. Psychosis is a hazardous and functionally disruptive psychiatric condition which may affect women in pregnancy, entailing negative consequences for maternofetal well-being. The precise pathophysiological basis and consequences of a psychotic episode in pregnancy remain to be further elucidated. The placenta is a pivotal tissue with many functions in the gestational period, critically influencing the fate and development of pregnancy. Although detrimental alterations have been observed in women undergoing severe psychiatric disorders in pregnancy, there are little studies evaluating the consequences of suffering from a psychotic episode in the placental tissue In this work, we have evaluated the histopathological consequences of a first episode of psychosis in pregnancy (FE-PW; N=22) and compare them with healthy pregnant women (HC-PW; N=20) by using histological, immunohistochemical and gene expression techniques. Our results define that the placental tissue of FE-PW display an increase in the number of placental villi, bridges, syncytial knots and syncytial knots/villi. Besides, we have also observed an enhanced gene and protein expression in FE-PW of the hypoxic marker HIF-1α, together with the apoptotic markers BAX and Bcl-2. To our knowledge, this is the first study demonstrating significant histopathological changes in the placenta of women suffering a new-onset psychotic episode in pregnancy. Further studies should be aimed at deepening the knowledge about the pernicious effects of psychosis in the maternofetal tissues, as well as the potential implications of these alterations.

Key words: Psychosis, Mental disorders, Pregnancy, Placenta, Maternofetal well-being, Histopathology

Corresponding Author: Miguel A. Ortega, Department of Medicine and Medical Specialities, Faculty of Medicine and Health Sciences, University of Alcalá, 28801 Alcalá de Henares, Spain. e-mail: miguel.angel.ortega92@gmail.com
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Introduction

Psychosis is a common and functionally disruptive symptom which represents an important target of evaluation and treatment in neurologic and psychiatric practice (Arciniegas, 2015). Neither the Diagnostic and Statistical Manual fifth edition (DSM-5) -the main guideline on psychiatric disorders-, nor the International

Classification of Diseases 11th edition (ICD-11) offer a formal definition of psychosis. However, they allow to define psychotic disorders by abnormalities in one of the following five domains: Delusions; hallucinations; disorganized thought; grossly disorganized or abnormal motor behavior (including catatonia) and negative symptoms (Calabrese and Khalili, 2022). Psychotic disorders can be either primary, with unknown causes or secondary to other medical conditions (Griswold et al., 2015). DSM-5 and ICD-11 follow a similar classification system of psychosis disorders, both recognizing a) schizotypal disorder; b) delusional disorder; c) schizophrenia; d) schizo-affective disorder and e) attenuated psychosis syndrome, which requires further research efforts (Gaebel and Zielasek, 2015; Biedermann and Fleischhacker, 2016).

Although it is notably rare, new-onset primary psychosis can occur in pregnancy. According to previous epidemiologic studies, the risk of developing a severe mental illness in pregnancy is around 7.1 in 10,000 women per year and the main risk factors identified for suffering from psychosis in pregnancy include family history of psychosis: previous history of psychosis in pregnancy and preexisting or undiagnosed psychotic/mood disorder (Watkins and Newport, 2009). New-onset psychiatric disorders during pregnancy represent an important challenge faced by the clinicians and pregnant women, as balancing the risks and benefits of symptoms and treatments is critical because both medication and maternal illness may have adverse effects on the fetus (Cott and Wisner, 2003; Karakasi et al., 2017; Friedman et al., 2018). To date, there are hardly any notions about the pathophysiological changes that occur in psychotic disorders. However, previous studies have claimed that pregnant women with psychosis have an elevated risk of multiple adverse obstetric and neonatal outcomes, such as cesarean delivery, antepartum/postpartum hemorrhage, poor fetal growth, fetal abnormalities, or stillbirth, among others (Zhong et al., 2018). Likewise, new-onset primary psychosis in pregnancy can also have long-term consequences for the mother, having been established that women with a history of psychotic disorder are at high risk of future psychiatric illness (Howard et al., 2004).

In this context, a further understanding of the pathobiological basis involved in maternofetal suffering due to primary psychotic disorders during pregnancy arise as a critical point of study in this field. In this sense, the contribution of the placenta to maternofetal distress observed in pregnant women with psychosis has not been explored yet. The placenta is a pivotal organ with many physiological functions during pregnancy. This structure is responsible for ensuring an adequate maternofetal exchange, fulfilling an important endocrine activity during pregnancy while acting as a mechanical, chemical, and immunological barrier, also determining maternofetal programming, even beyond pregnancy (Ortega et al., 2022a). Conversely, structural and functional changes of the placenta have been evidenced in multiple systemic and obstetric pathologies, entailing detrimental consequences for maternofetal well-being (Huppertz, 2011; Shang and Wen, 2018; Hendrix et al., 2020; Ortega et al., 2021, 2022b). Hence, unraveling the placental status observed in pregnant women who undergo a new-onset episode of acute psychosis during gestation would aid in understanding the implications of psychiatric disorders in maternofetal well-being. Having this goal, we analyzed the possible presence and patterns of histopathological lesions found in the placentas of these women and how they might be related to hypoxic or apoptotic events in comparison to healthy pregnant women (HC-PW).

Materials and methods

Design

In the present work, an observational, analytical, prospective study was carried out from 42 women in the last trimester of pregnancy. Of them, 22 with a clinical diagnosis of a first episode of psychosis (FE-PW) and 20 women with no history of FE (HC-PW), were included. The inclusion criteria included: (1) Psychiatrist-confirmed diagnosis of first episode of psychosis according to DSM-5 criteria, using the Structured Clinical Interview for DSM-5 (SCID-5) (First et al., 2015), (2) aged from 18 to 45 years and (3) fluent Spanish speaking that enables the assessment. The symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Exclusion criteria were: a) meeting diagnostic criteria for another current Axis-I mental disorder; b) meeting diagnostic criteria for intellectual disability; c) history of neurodevelopmental disorders or head injury with loss of consciousness. The median age in FE-PW group was 33.5 [21-42] years and 33.5 [25-39] years in HC-PW. The median gestational age for FE-PW women was 40 [38-41] weeks, and 40 [39-42] weeks for HC-PW. Clinical and demographic characteristics of these patients are in Table 1.

Previously to enrolment, each patient was properly informed, providing signed written consent. This work

Table 1. Clinical and demographic characteristics of women with first psychotic episode during pregnancy and healthy controls.

	FE-PW (n=22)	HC-PW (n=20)
Median age (IQR), years	33.5 (21-42)	33.5 (25-39)
Median gestational age (IQR), weeks	40 (38-41)	40 (39-42)
C-section delivery, n (%)	3 (13.6)	2 (10.0)
Previous pregnancies, n (%)	8 (36.4)	9 (45.0)
Previous abortions, n (%)	1 (4.5)	2 (10.0)
Regular menstrual cycles, n (%)	17 (77.3)	16 (80.0)
PANSS mean (SD)	Positive 18.8 (6.3) Negative 25.7 (7.9)	-----

FE-PW=first psychotic episode during pregnancy, HC-PW=healthy controls pregnant women.

passed the Clinical Research Ethics Committee of the Central University Hospital of Defense University of Alcalá (37/17) and was performed according to the ethical principles of autonomy, beneficence, non-maleficence and distributive justice, as well as following the regulations of Good Clinical Practice, the principles of Declaration of Helsinki (2013) and the Oviedo Convention (1997).

Tissue samples

Postpartum placental biopsies were collected from all 42 patients. For each patient sample, five placental pieces were obtained using a scalpel to include diverse mixed cotyledons and then they were separated in two different sterile tubes: one containing minimal essential medium (MEM; Thermo Fisher Scientific, Inc., Waltham, MA, USA) with 1% antibiotic/antimycotic (streptomycin, amphotericin B, and penicillin; Thermo Fisher Scientific, Inc.) and another with RNAlater® solution (Ambion; Thermo Fisher Scientific, Inc., Waltham, MA, USA). Thereafter, the samples were processed in a class II laminar flow hood (Telstar AV 30/70 Müller 220V 50MHz; Telstar; Azbil Corporation) in a sterile environment. Afterwards, samples were preserved in 1 ml of RNAlater® at -80°C for later processing for gene expression study. Then, conserved MEM samples were washed and rehydrated 5 times in MEM free of antibiotics to eliminate erythrocytes. Then, using a scalpel, they were divided into 2 cm fragments and fixed in F13 (60% ethanol, 20% methanol, 7% polyethylene glycol and 13% distilled water) according to previous protocols (Cristobal et al., 2018). Subsequently, paraffin-embedded samples were formed using molds. After the paraffin was solidified, an HM 350 S rotary microtome (Thermo Fisher Scientific, Inc., Waltham, MA, USA) was employed to obtain 5 µm thick sections. Thereafter, they were stretched in a hot water bath and collected on glass slides treated with 10% polylysine, facilitating the adherence of the sections. After paraffin inclusion and subsequent processes, the sections of the samples were subjected to different staining techniques (hematoxylin-eosin) and immuno-histologic techniques.

Gene studies

First, we extracted RNA through the guanidinium thiocyanate-phenol-chloroform method as described in previous studies (Ortega et al., 2021). This method allows the study of the mRNA expression levels of selected genes. Complementary DNA (cDNA) was synthesized by reverse transcription (RT) from 50 ng/µL of RNA samples. 4 µL of each sample was mixed with 4 µL of 0.25 µg/µL oligo-dT solution (Thermo Fisher Scientific, Inc., Waltham, MA, USA) and afterwards placed at 65°C for 10 min in a dry bath (AccuBlock, Labnet International Inc., NJ, USA) leading to the denaturation of RNA. The samples were then placed on ice and 10 µL of reverse transcription mix containing the following products: 2.8 µL of First Strand Buffer 5X (250 mM Tris-HCl and pH 8.3; 375 mM KCl:15 mM MgCl2) (Thermo Fisher Scientific, Inc., Waltham, MA, USA); 1 µl RT enzyme (all from Thermo Fisher Scientific, Inc., Waltham, MA, USA); 2 µl of 10 mM deoxyribonucleotide triphosphate; 2 µl of 0.1 M dithiothreitol; 1.7 µL of DNase and RNase free water; 0.5 µL of RNase inhibitor (RNase Out).

The reverse transcription process was performed with a G-Storm GS1 thermocycler (G-Storm Ltd.). The samples were then incubated at 37°C for one hour and fifteen min in order to facilitate cDNA synthesis. At this point, the temperature was raised up to 70°C and held for 15 min, causing reverse transcriptase denaturation. Subsequently, the temperature was gradually lowered to 4°C. Negative reverse transcription was equally carried out to ensure the absence of genomic DNA contamination in RNA samples, in which the M-MLV RT enzyme was substituted by DNase- and RNase-free water. cDNA produced at room temperature was diluted 1:20 in DNase- and RNase-free water and stored at -20°C until further use.

Specific primers for the selected genes (Table 2) were designed de novo through the Primer-BLAST and AutoDimer online applications (Ye et al., 2012; Vallone and Butler, 2004). TATA-box binding protein (TBP) gene, which is constitutively expressed, was used as a control to normalize the results (Jang et al., 2022). The gene expression units are expressed as relative quantities of mRNA. RT-qPCR was performed on a StepOnePlus™ System (Applied Biosystems; Thermo Fisher Scientific, Inc.) using the relative standard curve method. The reaction was completed as follows: 5 µL of sample -mixed at 1:20 with 10 µL iQ™ SYBR® Green Supermix (Bio-Rad Laboratories, Inc.)- was mixed with 1 µL each of forward and reverse primers, and 3 µL of DNase and RNase-free water, which were then added to a MicroAmp® 96-well plate (Applied Biosystems; Thermo

Table 2. Primers used for RT-qPCR: sequences and binding temperatures (Temp).

GENE	SEQUENCE Fwd (5´→3´)	SEQUENCE Rev (5´→3´)	Temp
TBP	TGCACAGGAGCCAAGAGTGAA	CACATCACAGCTCCCCACCA	60°C
Hif-1α	CACGGTCCACAGCTCATCAT	GGTTGGGGTCTTCTGTGGAG	59°C
BAX	AGGGGCCCTTTTGCTTCAG	TGTCCAGCCCATGATGGTTC	61°C
BCL-2	AAAAATACAACATCACAGAGGAAGT	TCCCGGTTATCGTACCCTGT	57°C

Fisher Scientific, Inc., Waltham, MA, USA). Thermocycling conditions were used: Initial denaturation for 10 min at 95°C, denaturation for 15 s at 95°C, annealing at variable temperatures depending on the melting temperature of each primer pair for 30 s, and elongation at 72°C for 1 min, for 40-45 cycles. Then, a dissociation curve for 15 s at 95°C, 1 min 60°C, 15 s 95°C, and 15 s 60°C was developed. Fluorescence detection was performed at the end of every repeat cycle (amplification) and at the different steps of the dissociation curve. The data collected from the aforementioned genes were included in a standard curve made by serial dilutions of a mixture of the samples, that were included in each plate according to the constitutive expression of TBP (in agreement with the manufacturer's protocols). This RT-qPCR was performed twice in all samples of placenta tissue.

Protein studies

Avidin-biotin complex with avidin peroxidase was used for antigen/antibody reactions detection (Ortega et al., 2021). Immunohistochemical studies were performed on placenta samples embedded in paraffin. The antibodies used are detailed in the protocol specifications (Table 3).

Placental tissues were incubated with the primary antibody for one hour and a half (Table 3). Subsequently, they was incubated with 3% BSA Blocker (cat. no. 37,525; Thermo Fisher Scientific, Inc., Waltham, MA, USA) and PBS (4°C overnight). Next day, placental samples were incubated with biotin-conjugated secondary antibody, previously diluted in PBS during one hour and a half at room temperature (Table 3). Thereafter, the avidin-peroxidase conjugate Extr-Avidin®-Peroxidase (Sigma-Aldrich; Merck KGaA, San Luis, MO, USA) was added for one hour at room temperature (1:200 dilution in PBS). Finally, chromogenic diaminobenzidine (DAB) substrate kit (cat. no. SK-4100; Maravai LifeSciences, CA, USA), was used to determine protein expression level. This kit was prepared immediately before exposure (5 mL distilled water; four drops DAB; two drops of hydrogen peroxide and two drops of buffer).

The use of the peroxidase chromogenic substrate for 15 min at room temperature allows the detection of the signal in form of brown stains. For each section, negative controls were assigned for the different proteins, replacing incubation with primary antibody for a PBS solution. Carazzi hematoxylin was used for 15

Table 3. Primary and secondary antibodies used and their dilutions.

Antigen	Species	Dilution	Provider	Protocol Specifications
Hif-1α [ESEE122]	Mouse monoclonal	1:250	Abcam (ab8366)	Triton 100×0.1% in PBS, 10 min
BAX [E63]	Rabbit monoclonal	1:750	Abcam (ab32503)	Glycine HCl, 30 min RT. 0.2% Hyaluronidase, 30 min 42°C
BCL-2 [EPR17509]	Rabbit monoclonal	1:200	Abcam (ab245410)	EDTA at pH9 before incubation with blocking solution
IgG (Rabbit)	Mouse	1:1000	Sigma-Aldrich (RG-96/B5283)	------
IgG (Mouse)	Goat	1:300	Sigma-Aldrich (F2012/045K6072)	------

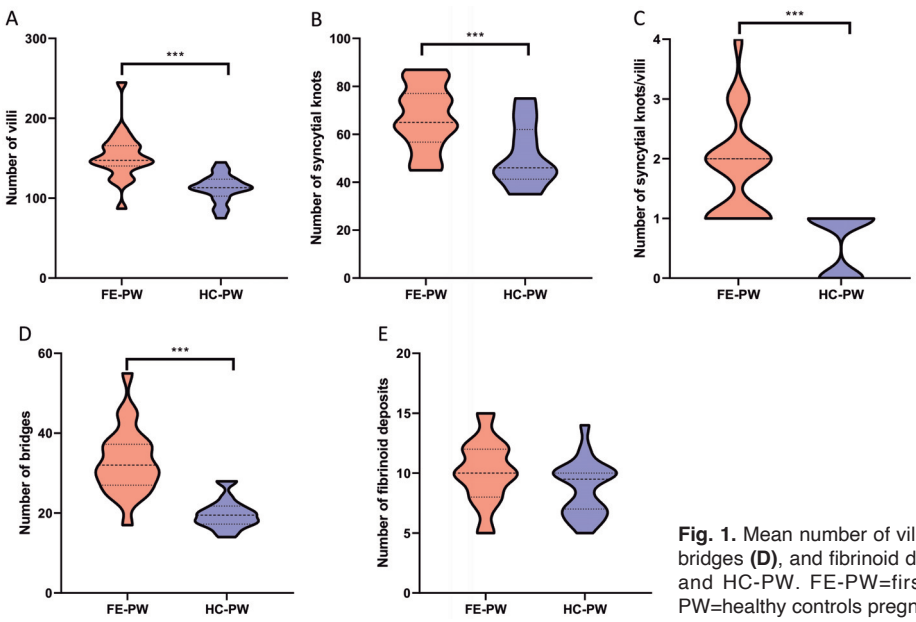

Fig. 1. Mean number of villi **(A)** syncytial knots **(B)**, syncytial knots/villi **(C)**, bridges **(D)**, and fibrinoid deposits **(E)** per field in the placenta from FE-PW and HC-PW. FE-PW=first psychotic episode during pregnancy, HC-PW=healthy controls pregnant women. ***p<0.001.

min to achieve contrast in all tissues.

Evaluation of expression and statistical analysis

Five different sections and ten areas of view were randomly examined for every patient of FE-PW and HC-PW groups. A patient was reported as positive when the stained mean area in the studied sample was ≥5% of the total, following the immunoreactive score (IRS) as established in previous studies (Ortega et al., 2022b). Immunostaining was evaluated by two independent histologists, and then each sample was scored using the following scale: 0-1, minimum staining (≤25%); 2, moderate staining (25-65%); and 3-4, strong staining (≥65-100%). A Zeiss Axiophot optical microscope (Carl Zeiss, Oberkochen, Germany) was used for the histological determination. For the treatment of statistical data, GraphPad Prism® v6.0 (GraphPad, Inc., San Diego, CA, USA) program was utilized. Mann-Whitney U test allows the comparison between both groups, being expressed as the median ± SD. Significant values were established as $p<0.05$ (*), $p<0.01$ (**), and $p<0.001$ (***).

Results

Placentas from women with a first psychotic episode during pregnancy show Tenney-Parker changes

Placentas from women with a first psychotic episode during pregnancy (FE-PW) show a significant increase in the number of villi compared to healthy controls (HC-PW) [FE-PW=152.727±30.253, HC-PW=112.550 ±17.470, $p<0.0001$, Figs. 1A, 2A,B]. We observed how these FE-PW placentas showed a significant increase in the number of syncytial knots in these villi compared to HC-PW [FE-PW=67.318±13.404, HC-PW=51.050± 12.947, $p=0.005$, Fig. 1B]. In this sense, we observed how the existing ratio between syncytial knots/villi was significantly higher in FE-PW placentas [FE-PW=1.818±0.853, HC-PW=0.600±0.503, $p<0.001$, Fig. 1C]. In addition, we observed that the number of bridges

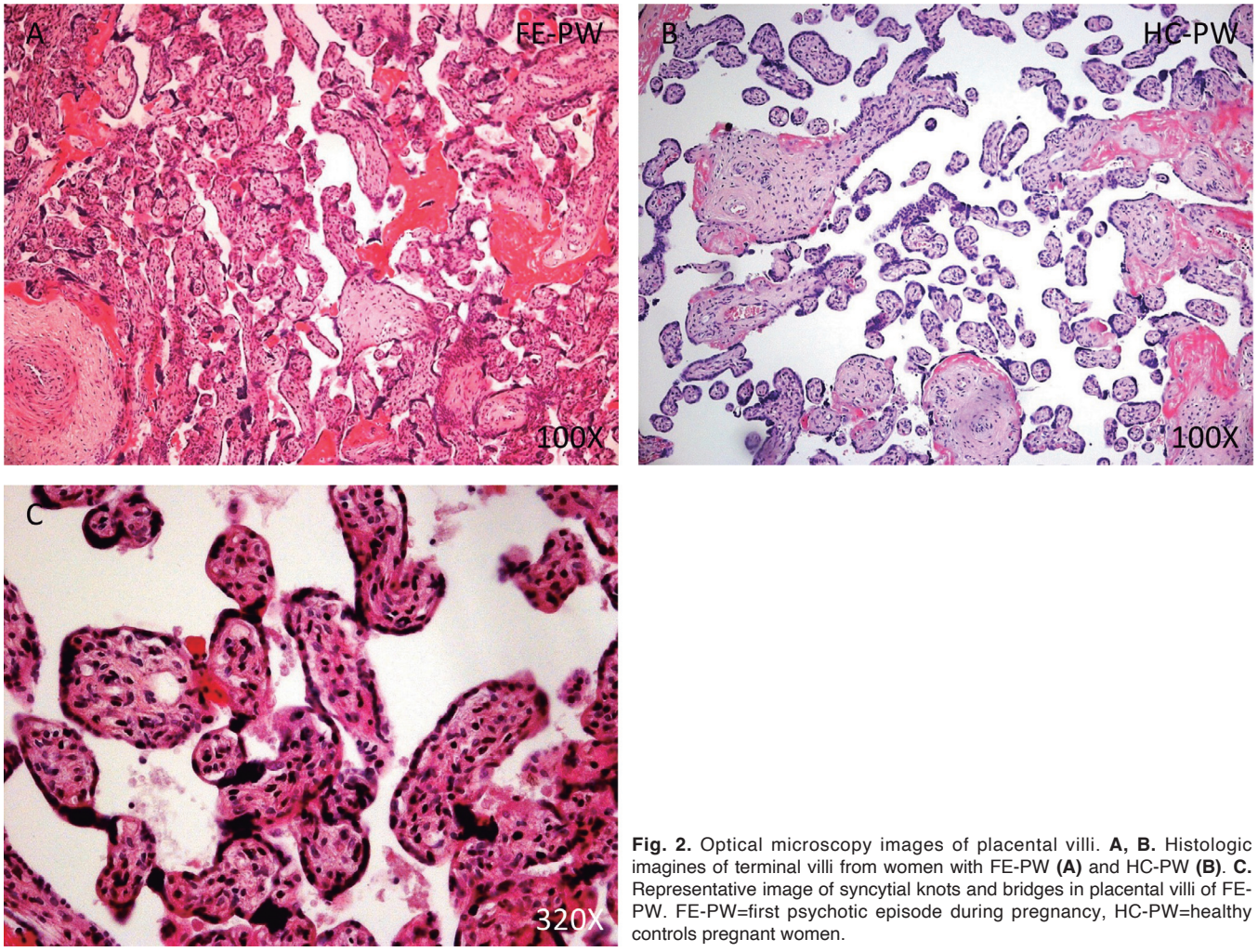

Fig. 2. Optical microscopy images of placental villi. **A, B.** Histologic imagines of terminal villi from women with FE-PW **(A)** and HC-PW **(B)**. **C.** Representative image of syncytial knots and bridges in placental villi of FE-PW. FE-PW=first psychotic episode during pregnancy, HC-PW=healthy controls pregnant women.

between the placental villi was significantly higher in FE-PW compared to HC-PW [FE-PW=33.000±8,452, HC-PW=19.750±3,726, p<0.001 , Figs. 1D, 2C]. In contrast, we did not observe significant differences in fibrinoid deposits in the placental villi of FE-PW and HC-PW [FE-PW=10.136±2.678, HC-PW=8.750±2.337, p=0.0810, Fig. 1E].

Placentas from women with a first psychotic episode during pregnancy show increased expression of markers of hypoxia

We observed a significant increase in the expression of hypoxia markers, such as Hif-1α in FE-PW placentas. We observed increased Hif-1α gene expression by RT-qPCR in placentas from FE-PW compared to HC-PW [FE-PW=6.493±1.697, HC-PW=4.260±1.530, p=0.0002, Fig. 3A]. The study of protein expression using immunohistochemical techniques showed an increase in Hif-1α expression in FE-PW placentas compared to HC-PW [FE-PW=2.455±0.611, HC-PW=1.313±0.617, p<0.0001, Fig. 3B]. The histological study showed how the expression of Hif-1α in the FE-PW placentas was located in the cells of the syncytiotrophoblast, cytotrophoblast and the fetal capillary compared to HC-PW (Fig. 3C,D).

Placentas from women with a first psychotic episode during pregnancy show increased expression of apoptotic markers

Our study shows how there is an increase in the expression of proapoptotic markers (BAX) and a decrease in antiapoptotic markers (Bcl-2) in FE-PW compared to HC-PW. We observed increased BAX gene expression by RT-qPCR in FE-PW compared to HC-PW placentas [FE-PW=6.370±1808, HC-PW=3.749±1431, p<0.0001, Fig. 4A]. The study of protein expression

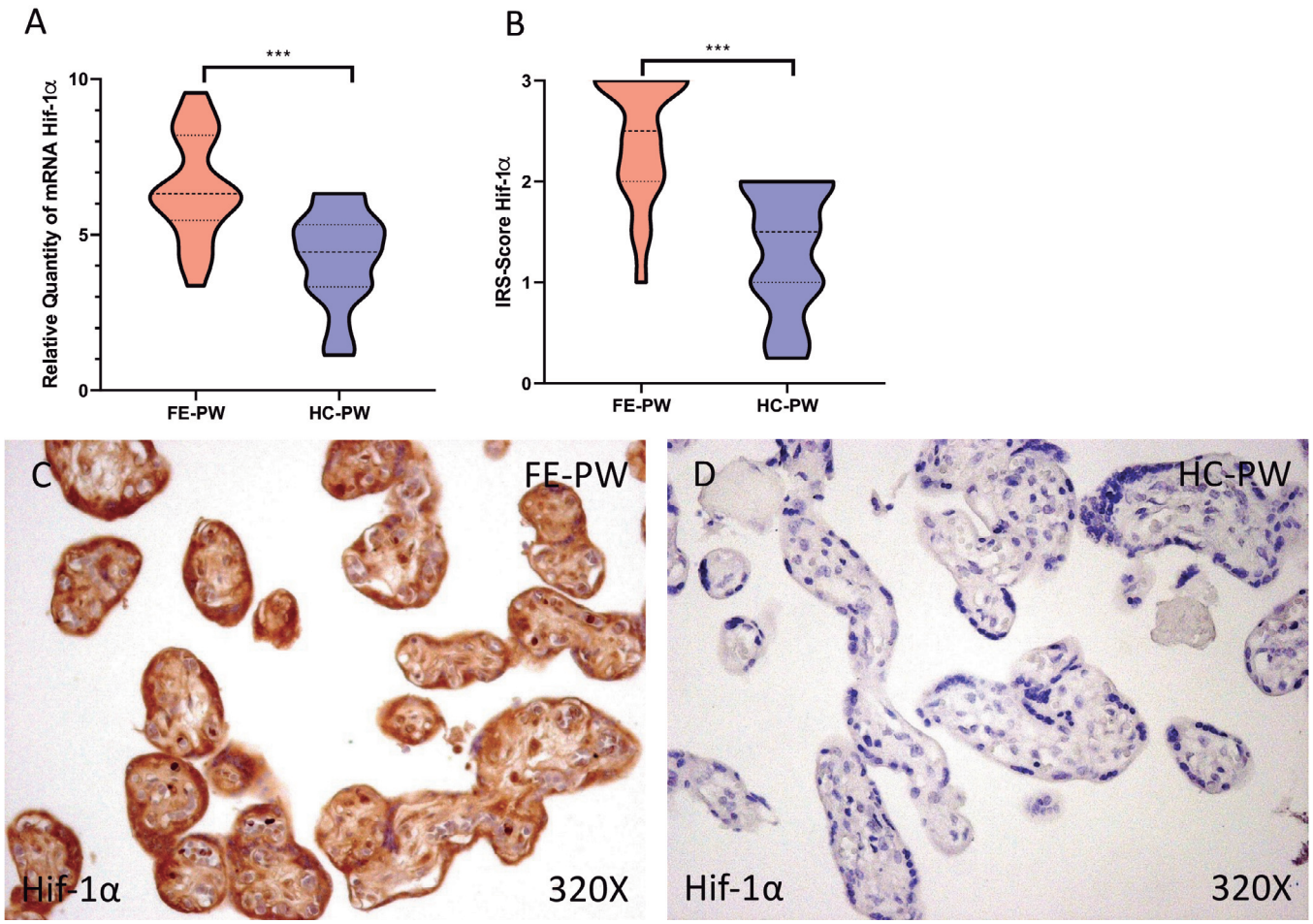

Fig. 3. A. Hif-1α mRNA expression in the FE-PW and HC-PW. **B.** IRS-Scores for Hif-1α in the placenta villi of the FE-PW and HC-PW. **C, D.** Images showing the immunostaining for Hif-1α in the FE-PW and HC-PW. FE-PW=first psychotic episode during pregnancy, HC-PW=healthy controls pregnant women. ***p<0.001.

using immunohistochemical techniques showed an increase in BAX expression in FE-PW placentas compared to HC-PW [FE-PW=2.034±0.729, HC-PW=1.325±0.608, p=0.0023, Fig. 4B]. The histological study showed how the expression of BAX in the FE-PW placentas was located in the cells of the syncytiotrophoblast, cytotrophoblast and the fetal capillary compared to HC-PW (Fig. 4C,D).

In contrast, we observed a significant decrease in Bcl-2 gene expression by RT-qPCR in FE-PW compared to HC-PW placentas [FE-PW=3.198±1.375, HC-PW=4.622±1.278, p=0.0029, Fig. 5A]. The study of protein expression using immunohistochemical techniques showed a significant decrease in Bcl-2 expression in FE-PW placentas compared to HC-PW [FE-PW=1.102±0.565, HC-PW=1.563±0.734, p=0.0338, Fig. 5B]. The histological study showed how the expression of Bcl-2 in the placentas of HC-PW was located in the cells of the syncytiotrophoblast, cytotrophoblast and the fetal capillary compared to FE-PW (Fig. 5C,D).

Discussion

For the first time, we have demonstrated that FE-PW display significant structural changes in the placenta tissue. In more detail, this organ seems to present a greater number of chorionic villi and syncytial knots/bridges, along with increased markers of apoptotic cellular death in comparison to HC-PW. Besides, this cellular damage seems to be accompanied with a hypoxic environment observed in this organ, having been demonstrated an augmented expression of the hypoxic marker HIF-1α. Our results are in agreement with previous works, which have found how different psychiatric disorders in pregnancy may lead to different structural and functional abnormalities in this organ, entailing detrimental consequences for maternofetal well-being (Kang-Yi et al., 2018; Lahti-Pulkkinen et al., 2018). In turn, behavioral and structural alterations in the placenta have been associated with an increased risk of suffering from future neuropsychiatric disorders in the fetus (Lahti-Pulkkinen et al., 2018; Kratimenos and

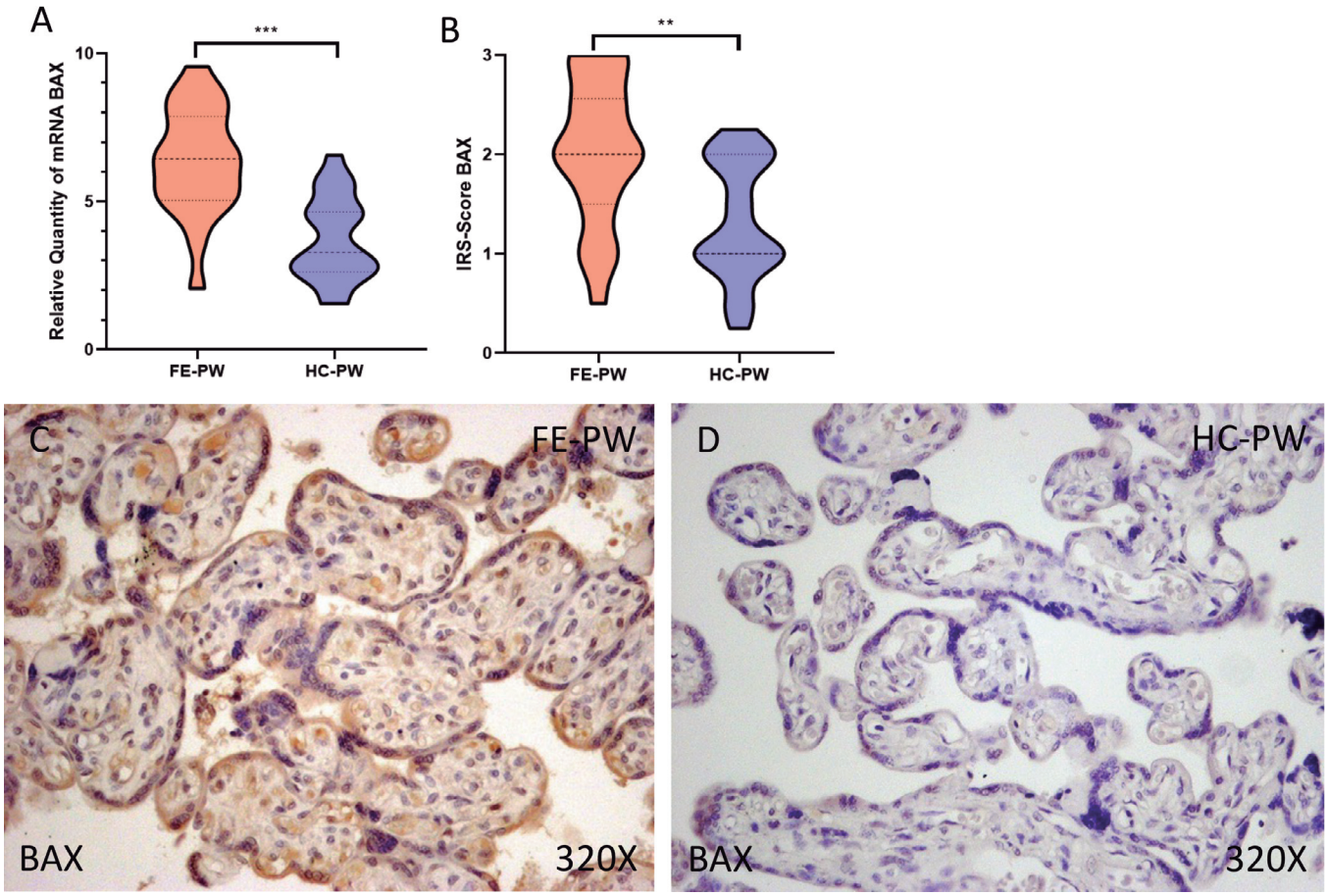

Fig. 4. A. BAX mRNA expression in the FE-PW and HC-PW. **B.** IRS-Scores for BAX in the placenta villi of the FE-PW and HC-PW. **C, D.** Images showing the immunostaining for Hif-1α in the FE-PW and HC-PW. FE-PW=first psychotic episode during pregnancy, HC-PW=healthy controls pregnant women. ***p<0.001.

Penn, 2019; Tesfaye et al., 2021), thus denoting the impact of different maternal psychiatric disorders in pregnancy for the placenta and the fetus.

Firstly, we have observed an augmented number of chorionic villi, syncytial knots (Tenney-Parker changes) and bridges in FE-PW when compared to HC-PW. Chorionic villi are the major structural and functional unit of the placenta (Wang and Zhao, 2010). Pathologically, an increased number of placental villi is tightly linked to hypoxic phenomena (García-Honduvilla et al., 2018; Ortega et al., 2018). The presence of syncytial knots tends to increase throughout pregnancy, although an augmented detection of them is also associated with conditions of uteroplacental malperfusion and are important in placental examination (Loukeris et al., 2010). Indeed, the presence of Tenney-Parker changes are observed in multiple pregnancy complications, showing evidence of oxidative damage and impaired transcriptional activity (Fogarty et al., 2013). Therefore, these structural changes may be an indicator of placental damage observed in FE-PW, which could be associated with the observed hypoxia.

A hypoxic environment plays multiple pivotal roles in early pregnancy, positively promoting fetal and placental development and growth (Kojima et al., 2022). Conversely, in middle and late pregnancy, a marked hypoxia is typically related to vascular remodeling, oxidative stress, metabolic changes, mitochondrial dysfunction and endoplasmic reticular stress, which is observed in multiple disease conditions (Van Patot et al., 2012; Ortega et al., 2023). HIF-1α is a major orchestrator of the hypoxic responses, modulating a wide variety of downstream products and signaling molecules (Zamudio et al., 2007; Siragher and Sferruzzi-Perri, 2021). Previous studies have found that high expression levels of HIF appear to be associated with enhanced

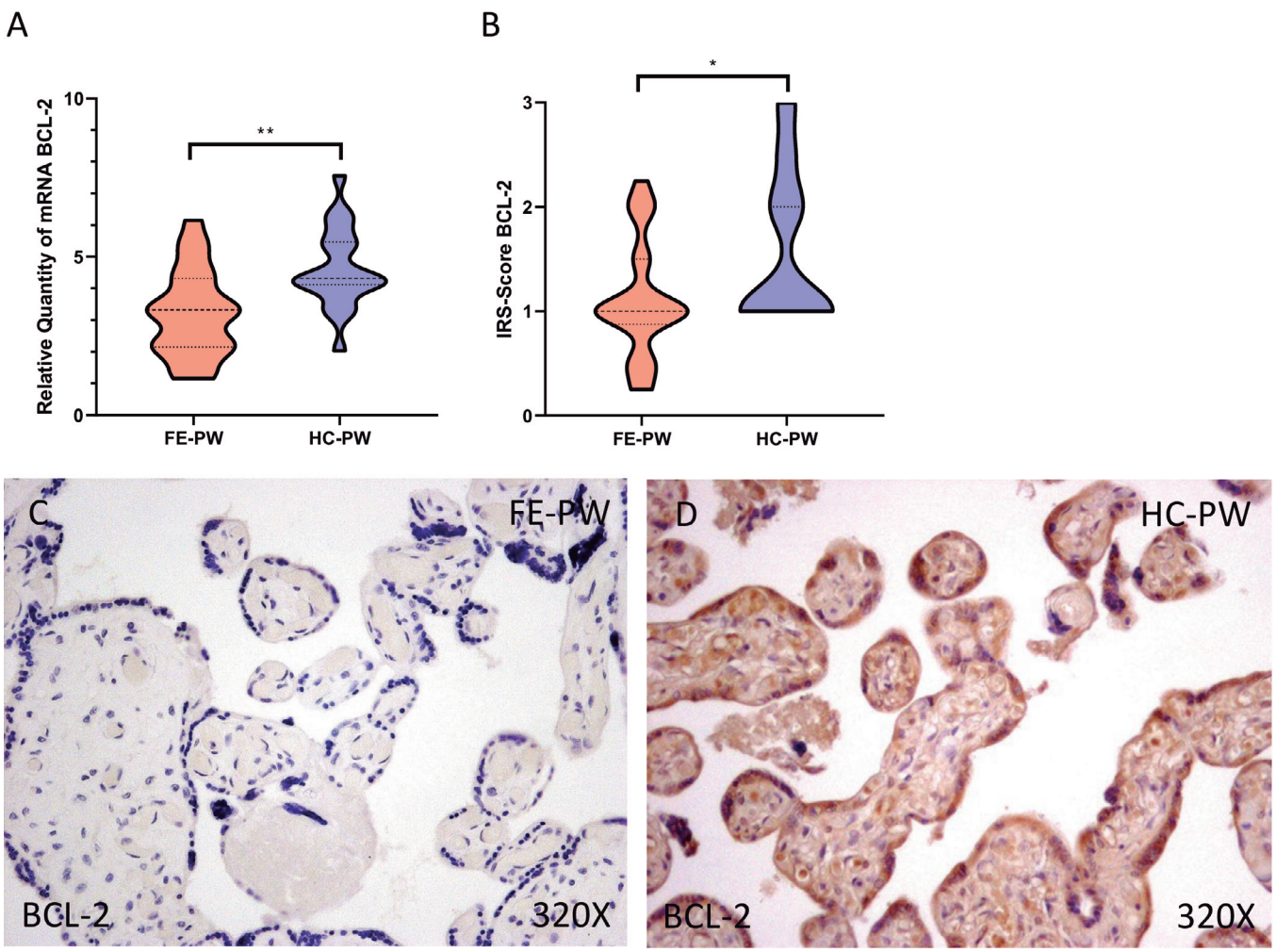

Fig. 5. A. Bcl-2 mRNA expression in the FE-PW and HC-PW. **B.** IRS-Scores for Hif-1α in the placenta villi of the FE-PW and HC-PW. **C, D.** Images showing the immunostaining for Bcl-2 in the FE-PW and HC-PW. FE-PW=first psychotic episode during pregnancy, HC-PW=healthy controls pregnant women. *p<0.05, **p<0.01.

trophoblastic apoptosis under pathological environment (Zhang et al., 2020). An aberrant expression of the apoptotic markers BAX and Bcl-2 might support the notion that the apoptotic process is altered in the placenta of FE-PW. Although the apoptosis is more marked as pregnancy progresses, an altered expression of BAX and Bcl-2 has been observed in different conditions associated with placental damage and suffering (De Falco et al., 2001; Sgarbosa et al., 2006; Cobellis et al., 2007; García-Honduvilla et al., 2018). Collectively, these morphological changes in the structure and behavior of the placenta might be an indicator of tissue damage observed in FE-PW, which may be potentially involved in the maternofetal consequences of this psychiatric disorder.

Conclusions

In the present research, we show evidence of an augmented number of chorionic villi, syncytial knots/bridges along with an enhanced hypoxia and apoptotic death observed in the placental tissue of FE-PW. To our knowledge, this is the first work reporting histological changes in this organ. Further studies are needed to deepen knowledge of the differential signatures of the placenta tissue in women affected by this rare but pernicious psychiatric disorder.

Author Contributions. All authors have read and agreed to the published version of the manu-script.

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Institutional Review Board Statement. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Clinical Investigations of the Central University Hospital of Defense Gómez-Ulla-UAH (03-37/17 on 03 March 2017).

Informed Consent Statement. Informed consent was obtained from all subjects involved in the study.

Data Availability Statement. The data used to support the findings of the present study are available from the corresponding author upon request.

Conflicts of Interest: The authors declare no conflict of interest.

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