

# Histogenesis of White Pulp of the Human Foetal Spleen at Different Gestational Age Groups: A Cross-sectional Study

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## ABSTRACT

**Introduction:** The spleen is a highly vascular, ductless and the largest lymphoid organ in our body. Its functions include phagocytosis and immune responses. In the foetus, haematopoiesis is the primary function of the spleen, which regresses after birth; however, the production of lymphocytes continues after birth.

**Aim:** To investigate the histological changes in the immune component, specifically the White Pulp (WP), of the human foetal spleen at various gestational age groups.

**Materials and Methods:** The present cross-sectional histological study was conducted in the Department of Anatomy, Government KAPV Medical College, Trichy, Tamil Nadu, India, from July 2019 to December 2021. Study was carried out on 50 samples of aborted human foetuses between 10 weeks and 40 weeks of gestational age, without any obvious congenital abnormalities, in a South Indian population. The samples were collected from the Department of Obstetrics and Gynaecology at Government Mahatma Gandhi Memorial Hospital, Trichy, Tamil Nadu, India, after obtaining institutional ethical clearance and consent from the mothers. After processing the splenic tissues, slides were

prepared and stained with Haematoxylin and Eosin (H&E). The slides were observed under a compound light microscope using 4x, 10x, 40x and 100x magnifications. The appearance of lymphocytes, their developmental growth, and changes in WP were observed and interpreted. Statistical analysis was performed by computing the mean number of lymphoid follicles across gestational age groups using Statistical Package for the Social Sciences (SPSS) software version 21.0.

**Results:** Among the 50 foetuses, the capsule appeared between the 10<sup>th</sup> and 12<sup>th</sup> weeks, and trabeculae appeared at the 18<sup>th</sup> week. Lymphocytes were first observed at the 14<sup>th</sup> week, and lymphoid aggregation around the arteriole began at 22-24 weeks. The Periarterolar Lymphatic Sheath (PALS) was observed at the 24<sup>th</sup> week, with definite WP noted at 36 weeks. Vascular loops appeared at the 12<sup>th</sup> week, and the vascularity of the WP increased with the age of gestation.

**Conclusion:** The present study provides detailed knowledge of the histogenesis of the WP of the spleen, which is valuable for anatomists and pathologists. The foetal spleen exhibits high vascularity, suggesting its potential use for transplantation in cases of splenectomy in the future.

**Keywords:** Central arteriole, Eccentric, Follicle, Lymphocyte, Nodules

## INTRODUCTION

The spleen is a secondary lymphoid organ that plays a role in foetal haematopoiesis and immunomodulation. Haematopoietic function of the spleen continues throughout the foetal period and regresses after birth; however, the production of lymphocytes continues in postnatal life [1]. The spleen arises from the mesenchymal proliferation of the mesogastrium during the fifth week of gestation and reaches its definitive morphological structure during the third month [2]. The spleen is termed the graveyard of Red Blood Cells (RBCs), as it destroys aged RBCs; splenic macrophages engulf any blood-borne antigens. Foetuses exposed to antigen-related diseases undergo morphological changes in lymphoid organs, presumably as a consequence of the primary foetal immune reaction. These changes are characterised by an increase in the number of lymphoblasts and partly of macrophages in the spleen and lymph nodes. Exposure of foetuses to antigen-related diseases appears to cause marked changes in the normal development of lymphoid organs [3].

The splenic parenchyma is divided into two components: white pulp (WP) and red pulp. The WP occupies 5% to 20% of splenic tissue and mainly contains lymphocytes. The WP is subdivided into the PALS, follicles, and the marginal zone. Through the hilum, the splenic artery enters, branches, and then passes into the splenic parenchyma via the trabeculae of the spleen. When it enters the WP, it is called the central artery [4].

The PALS are lymphocyte aggregates around the central artery. PALS appear expanded in places due to the aggregation of B

lymphocytes, resembling lymphatic follicles. They are visible as white, semiopaque dots to the naked eye on a freshly cut spleen and are usually situated near the terminal arterioles. These nodules displace the central artery to an eccentric position, which differentiates the spleen from the lymph node [5].

The PALS and follicles are centres for lymphoid aggregation and proliferation. After antigenic stimulation, there is intense B cell proliferation and the development of germinal centres similar to those found in lymph nodes. Antigen-presenting dendritic cells present in the follicles are responsible for this germinal centre formation. Within 24 hours after antigenic stimulus, these germinal centres become very large and are visible to the naked eye. They are called splenic nodules or Malpighian corpuscles. When antigenic stimulation abates, the germinal centre regresses [6].

The marginal zone, or perifollicular zone, is located at the periphery of PALS, in between the red pulp and WP. It is considered a separate compartment and not part of the WP. From this site, many lymphocytes leave the circulation and migrate into the appropriate B and T lymphocyte aggregations. Here, lymphocytes are loosely arranged between a dense network of reticular fibres and reticular cells [7]. The role of the marginal zone is to identify blood-borne antigens and pathogens present in systemic circulation, which activate antigenic reactions [8].

According to Vellguth S et al., the development of the foetal spleen is described in the following three stages [1]: In the preliminary stage, erythroblasts, normoblasts and macrophages are observed.

In the transformation stage (15<sup>th</sup>-18<sup>th</sup> week), splenic lobules begin to form, consisting of a central artery surrounded by sheaths of lightly stained stationary cells like myofibroblasts. In the stage of lymphoid colonisation (18-24 weeks), WP started to develop at the 18<sup>th</sup> week of gestation. Accumulation of lymphocytes around the central arterioles (PALS) is seen around the 19<sup>th</sup>-20<sup>th</sup> week. Primary follicles assemble at the periphery of PALS. In the present study, the authors aimed to find out the histological changes in the WP of the human foetal spleen across various gestational age groups. The present study is compared with national and international studies based on the appearance of lymphoid follicles, the diameter of the lymphoid follicles, the development of the central arteriole, PALS and the marginal zone.

## MATERIALS AND METHODS

The present cross-sectional histological study was conducted in the Department of Anatomy, Government KAPV Medical College, Trichy, Tamil Nadu, India, from July 2019 to December 2021. Ethical committee approval was obtained from the Institutional Ethical Committee (IEC No. 16/2020).

**Inclusion criteria:** Human foetuses aborted or stillborn, with a gestational age between 10 weeks and 40 weeks, were included in the study.

**Exclusion criteria:** Foetuses less than 10 weeks old and those with major congenital anomalies, such as omphalocele, were excluded from the study.

### Study Procedure

Fifty samples of human foetuses [Table/Fig-1] were collected from the Department of Obstetrics and Gynaecology at Mahatma Gandhi Memorial Hospital, Trichy, Tamil Nadu, India, after obtaining prior consent from the mothers. The study samples were arbitrarily divided into five groups according to gestational age:



[Table/Fig-1]: Samples of 50 foetuses.

Group I: 10-15 weeks;

Group II: 15-20 weeks;

Group III: 21-25 weeks;

Group IV: 26-32 weeks;

Group V: 33-40 weeks.

In each group, 10 foetuses were studied. The gestational age of the foetuses was determined based on the last menstrual period and ultrasonogram reports from antenatal cases in the medical records during the collection. The age was confirmed by Crown Rump Length (CRL) calculation. The collected foetuses were preserved in 10% formalin for 15-20 days. Dissection of the foetuses was performed following the standard protocol described by Enid Gilbert Barness for foetal autopsy.

After dissection, the spleen was kept in 10% neutral buffered formalin for 2-4 days. The spleen was processed using the following technique: 1) tissue fixation; 2) tissue cutting; 3) dehydration; 4) clearing; 5) embedding; 6) microtomy and sectioning of the tissue block. Splenic tissues were processed for H&E staining. All sections were examined under a binocular light microscope, and

photographs were taken using a USB camera. All the photographs were studied and analysed.

Ocular and stage micrometer were used to measure the diameter of the lymphoid follicles. The shape of the lymphoid follicles in the spleen is either oval or spherical, so two measurements were taken: one for the vertical diameter and another for the transverse diameter. The diameter of the lymphoid follicle was calculated as follows:

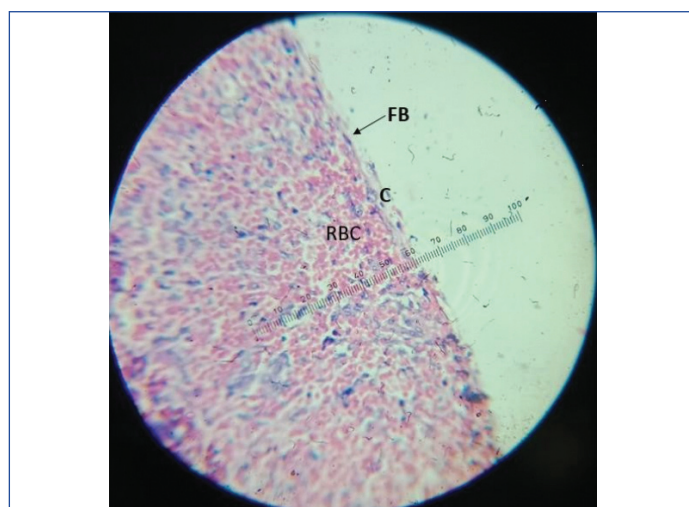
Diameter of lymphoid follicle= (maximum transverse diameter + maximum vertical diameter) ÷ 2.

The average diameter values were calculated in millimeters by converting measurements from the ocular micrometer to the stage micrometer.

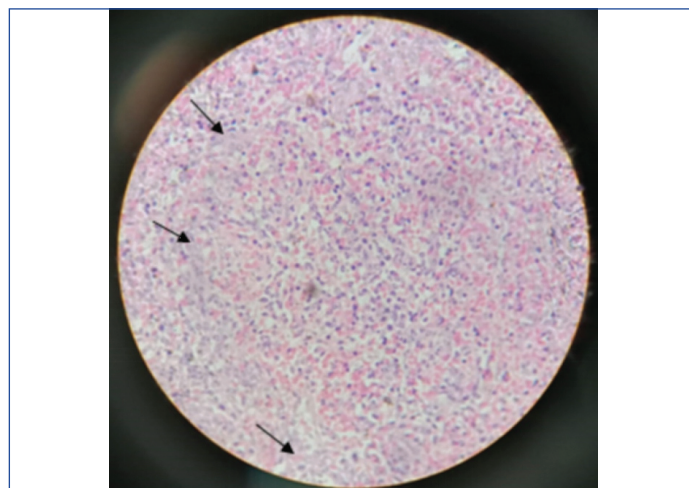
## RESULTS

In 50 foetuses, the observations were categorised into five groups based on gestational age.

**Group I (10-15 weeks):** Lymphocytes were diffusely present in the parenchyma of the spleen. Definite WP not formed in this group [Table/Fig-2]. In the 14<sup>th</sup> week, lymphocytes appeared in a scattered manner [Table/Fig-3].



[Table/Fig-2]: A 10<sup>th</sup> week foetus reveals a thin capsule (C) with flat fibroblast (FB) cells (H&E, 40x).

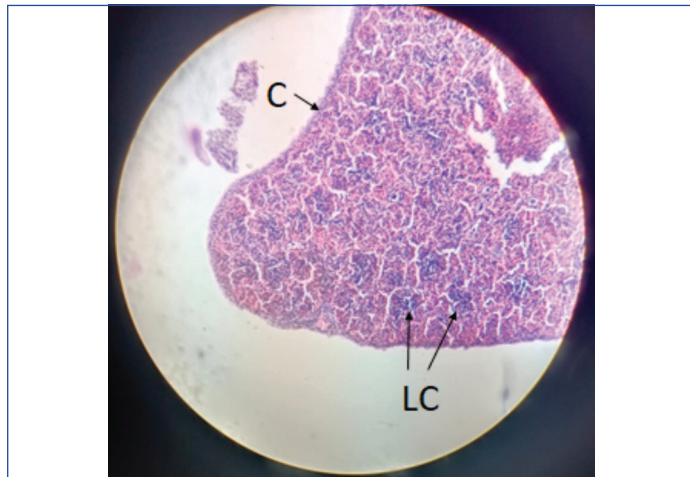


[Table/Fig-3]: In the 14<sup>th</sup> week foetus showing the appearance of lymphocytes (arrows) (H&E, 40x).

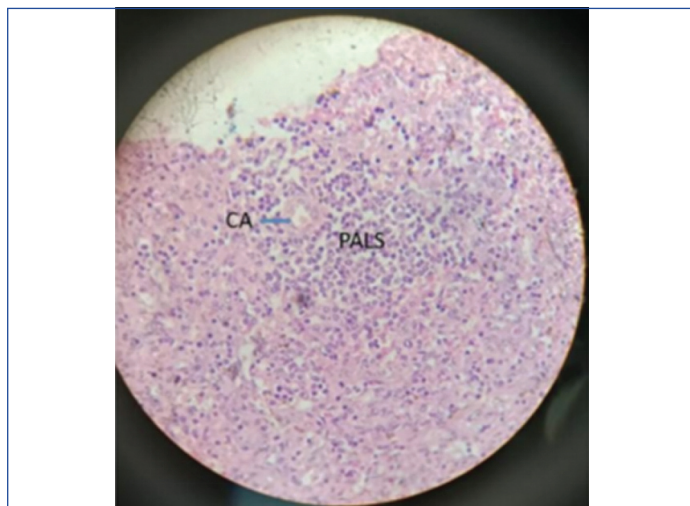
**Group II (16-20 weeks):** A few lymphocytes appeared in small groups and had no central arterioles [Table/Fig-4]. There were no dense, well-demarcated lymphoid aggregations, so definite WP did not develop in this group. There was no clear demarcation between the red pulp and WP. PALS began to form, and lymphocyte differentiation started to appear around the arterioles.

**Group III (21-25 weeks):** Lymphoid aggregations differentiated around the central arterioles to form PALS [Table/Fig-5]. The number of lymphoid

aggregations increased, but they were not compactly arranged. There was no clear demarcation with the surrounding tissues. Centrally placed arterioles with lymphoid follicles were recognised. The WP region consisted of a greater number of reticular fibres than the red pulp.

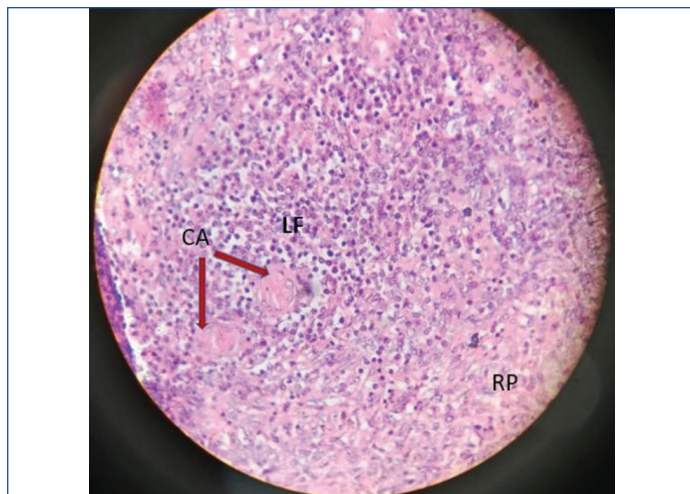


**[Table/Fig-4]:** A 16<sup>th</sup> week foetus showing capsule (C) with no trabeculae. Lymphocytes (LC) are arranged in small groups and are scattered without Central Arterioles (CA) (H&E, 10x).

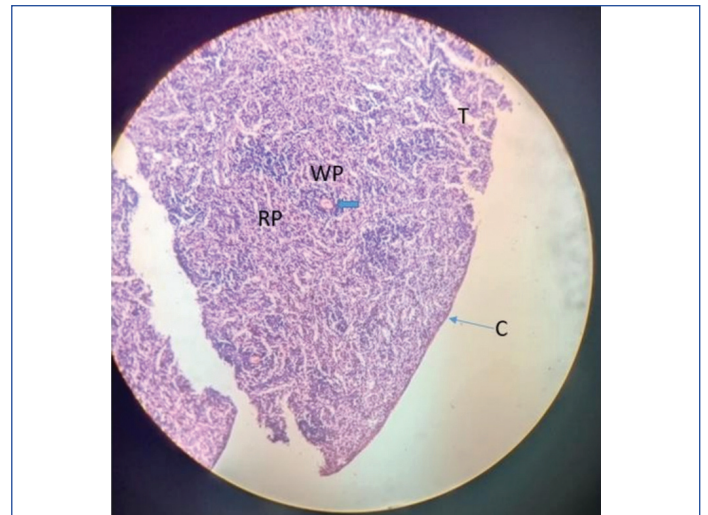


**[Table/Fig-5]:** A 24<sup>th</sup> week foetus showing the Periarterial Lymphatic Sheath (PALS) with Central Arterioles (CA) (H&E, 10x).

**Group IV (26-32 weeks):** Definite WP formed at the 28<sup>th</sup> week. Lymphocytes were compactly arranged to form lymphatic nodules. At the 30<sup>th</sup> week, a marginal zone appeared between the red pulp and WP. A few follicles showed double central arterioles [Table/Fig-6]. Well-established lymphatic follicles with central arterioles were observed [Table/Fig-7].

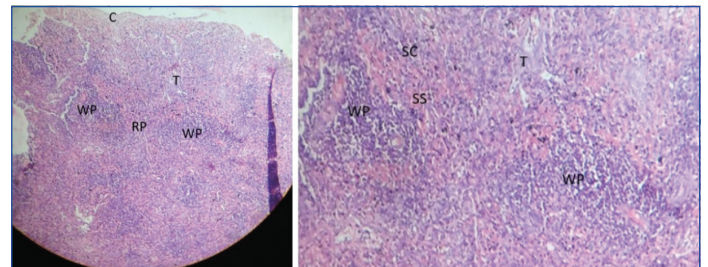


**[Table/Fig-6]:** A 30<sup>th</sup> week foetus showing a Lymphoid Follicle (LF) with two Central Arterioles (CA) and Red Pulp (RP) (H&E, 10x).



**[Table/Fig-7]:** A 32<sup>nd</sup> week foetus showing a thick capsule (C) and White Pulp (WP) with Central Arteriole (CA) (H&E, 10x).

**Group V (33-40 weeks):** At the 34<sup>th</sup> week, well-defined WP with clear differentiation from the surrounding area was observed. Both the size and the number of WPs increased. The number of lymphocytes in the red pulp area decreased. The WP exhibited matured lymphoid follicles with eccentrically placed arterioles [Table/Fig-8]. Well-demarcated Malpighian corpuscles were observed. At the 38<sup>th</sup> week, well-demarcated multiple WP components were observed. Lymphoid follicles were compactly arranged with densely aggregated lymphocytes and peripheral arterioles. Germinal centre not yet formed by term. Between the 38<sup>th</sup> and 40<sup>th</sup> weeks, the splenic structures resembled those of an adult spleen, without germinal centres. Changes in WP were observed and tabulated by group [Table/Fig-9]. Definite lymphoid follicles began to form from 30 weeks onward. [Table/Fig-10] shows the dimensions of lymphoid follicles in Groups IV and V.



**[Table/Fig-8]:** In a 38<sup>th</sup> week foetus showing White Pulp (WP) shows eccentrically placed arterioles (SS: Splenic sinusoids; SC: Splenic cords) (H&E, 40x).

Groups	Gestational age (weeks)	White Pulp (WP) changes
I	10-15	Lymphocytes appeared in parenchyma
II	15-20	Small groups of lymphocyte appeared and arranged in Scattered manner
III	21-25	Lymphocytes aggregation begins around the arteriole and form PALS
IV	26-32	Definite Lymphoid follicles started to form.
V	33-40	Well-defined WP and clear differentiation from surrounding area observed.

**[Table/Fig-9]:** White Pulp (WP) changes in different groups.

Gestational age (weeks)	Diameter of lymphoid follicle (in mm) (40x)
30	0.22
32	0.26
34	0.30
36	0.33
38	0.28

**[Table/Fig-10]:** Diameter of the lymphoid follicles in 30-38 weeks of gestational ages.

## DISCUSSION

According to Pal M et al., lymphocytes are observed in the parenchyma of the spleen at the 16<sup>th</sup> week; by the 17<sup>th</sup> week, lymphoid aggregations around the arterioles had started, but they were not well-defined [9]. Between the 26<sup>th</sup> and 30<sup>th</sup> weeks, the density of lymphocytic aggregation increased, but there was no clear line of demarcation from the surrounding area. Lymphoid follicles were well-defined between the 31<sup>st</sup> and 35<sup>th</sup> weeks of gestation. Between the 36<sup>th</sup> and 40<sup>th</sup> weeks, a greater number of well-defined WPs were observed, with clear demarcation from the surrounding tissue. This study closely correlates with the present study; lymphocytes appeared at the 14<sup>th</sup> week, lymphoid aggregation started at the 18<sup>th</sup> week, and well-defined WP formed at the 34<sup>th</sup> week.

Yatagiri SV et al., says that, at 17<sup>th</sup> week, lymphocytes were seen around central arterioles. By 20<sup>th</sup> week, PALS was noted. Between 24-30<sup>th</sup> week, central arteriole becomes eccentrically placed. During 36-40 weeks, well-marked white pulp was seen [10]. In the present study, the splenic lobule appeared at the 18<sup>th</sup> week. WP begins to develop into the lymphoid colonisation stage between the 18<sup>th</sup> and 24<sup>th</sup> weeks, and PALS forms between the 19<sup>th</sup> and 29<sup>th</sup> weeks. The assembly of primary follicles around PALS starts at the 23<sup>rd</sup> week, and the B lymphocytic region consists of specific stationary cells. In the present study, PALS started to form at the 22<sup>nd</sup> week. This finding closely agrees with the current study.

Alex L et al., state that at the 24<sup>th</sup> week of gestation, a few scattered lymphocytes appeared in mesenchymal tissues, which is the earliest feature of WP formation [11]. Eccentrically placed arterioles were observed at this stage, and more than one arteriole was seen in most of the follicles. This finding closely correlates with the present study, where two central arterioles [Table/Fig-6] were observed in Group IV from the 28<sup>th</sup> to 30<sup>th</sup> weeks.

Mukhia R et al., report that lymphocytic aggregation starts at the 17<sup>th</sup> week and that PALS are observed at the 20<sup>th</sup> week; lymphoid follicles were seen between the 21<sup>st</sup> and 25<sup>th</sup> weeks [12]. Lymphoid follicles are well-defined at the 34<sup>th</sup> week, and eccentrically placed arterioles are noted at the 36<sup>th</sup> week. These study findings are similar to those of the present study, where lymphoid aggregation starts at the 18<sup>th</sup> week, PALS are observed at the 22<sup>nd</sup> week, and lymphoid follicles are recognised in Group III between the 21<sup>st</sup> and 25<sup>th</sup> weeks. Well-defined and eccentrically placed arterioles are observed at the 36<sup>th</sup> week.

Holkunde A and Sakhare S states that lymphoblasts are arranged in scattered groups between the 14<sup>th</sup> and 18<sup>th</sup> weeks. In the present study, scattered groups were seen in the 16<sup>th</sup> week, and PALS were noticed around the 20<sup>th</sup> week; in the present study, PALS were observed at the 22<sup>nd</sup> week [13]. Between the 22<sup>nd</sup> and 38<sup>th</sup> weeks, lymphocytes were compactly arranged, and the arterioles were eccentrically placed. In the current study, from the 28<sup>th</sup> week onward, lymphocytes were compactly arranged to form lymphatic nodules, and eccentrically placed arterioles were noted at the 36<sup>th</sup> week, which closely agrees with findings from the Holkunde A and Sakhare S study [13].

Haldar A et al., state that up to the 14<sup>th</sup> week, the formative stage of WP will not be visible, which is the same as in the current study [14]. At the 16<sup>th</sup> week, scattered lymphocytes are observed, and a few formative stages of WP are noted; in the current study, at the 16<sup>th</sup> week, a few lymphocytes appear in small groups, and these groups are scattered. There is no definite WP seen between the 18<sup>th</sup> and 22<sup>nd</sup> weeks; in the present study, up to Group II (21-25 weeks), definite WP was not observed. WP is more prominent at the 26<sup>th</sup> week, and definite WP was observed at the 36<sup>th</sup> week. Between the 32<sup>nd</sup> and 36<sup>th</sup> weeks, prominent WP and definite lymphatic nodules with eccentrically placed arterioles were noticed. Definite WP and eccentrically placed arterioles were

observed at the 36<sup>th</sup> week. All findings of this study closely relate to the present study.

Srivani D and Pillai JJ state that during the 16<sup>th</sup> to 20<sup>th</sup> weeks of gestation, diffuse lymphoid aggregation was noted, but well-defined lymphoid follicles, central arterioles, and definite WP were not observed at this stage. Accumulation of lymphocytes around the arterioles to form lymphoid follicles was noted [15]. In the present study, diffuse lymphoid aggregation occurs at the 18<sup>th</sup> week. During the 25<sup>th</sup> to 32<sup>nd</sup> weeks, well-defined lymphoid follicles are seen, and PALS were observed. In the present study, PALS start to form at the 22<sup>nd</sup> week and are well-developed by the 24<sup>th</sup> week. From the 33<sup>rd</sup> week to term, lymphoid aggregation with eccentrically located arterioles was seen, and an increase in the size of the WP region was noted. In the present study, lymphoid aggregation with an eccentrically located central arteriole was observed at the 36<sup>th</sup> week. This study nearly correlates with the present study.

Yatagiri SV et al., state that at the 17<sup>th</sup> week, lymphocytes are seen around central arterioles. By the 20<sup>th</sup> week, PALS are noted [16]. Between the 24<sup>th</sup> and 30<sup>th</sup> weeks, the central arteriole becomes eccentrically placed along with ring fibre. During the 36<sup>th</sup>-40<sup>th</sup> weeks, well-marked WP is seen. In the present study, only a minimal number of lymphocytes are observed at the 18<sup>th</sup> week, PALS are noticed at the 22<sup>nd</sup> week, and definite WP is noted at the 36<sup>th</sup> week. These study findings are in greater agreement with the present study.

Thomas S et al., state that at the 20<sup>th</sup> week of gestation, lymphoid aggregation starts around arterioles, and PALS form at the 24<sup>th</sup> week, similar to the present study [17]. Two central arterioles were observed in a single lymphoid follicle at around the 28<sup>th</sup> week. During the 32<sup>nd</sup> week, a greater number of arterioles were surrounded by lymphoid aggregation; in our study, two central arterioles were observed between the 28<sup>th</sup> and 30<sup>th</sup> weeks. These primary lymphoid follicles were well differentiated from the neighboring tissues at the 37<sup>th</sup> to 40<sup>th</sup> weeks; in the present study, well demarcation was observed from neighboring tissues at the 36<sup>th</sup> week, which also agrees with the present study.

Souza AD et al., state that during the 10<sup>th</sup> week, lymphocytes were scattered throughout; in the present study, lymphocytes appeared scattered by the 14<sup>th</sup> week [18]. No central arterioles were noted until the 12<sup>th</sup> week; in our study, central arterioles were not observed until the 17<sup>th</sup> week. During the second trimester, lymphoid aggregation began. PALS were formed at the 20<sup>th</sup> week, and WP with lymphoid follicles were seen around the 23<sup>rd</sup> week. Well-developed follicles with central arterioles were observed at the 30<sup>th</sup> week; by the 36<sup>th</sup> week, central arterioles moved to an eccentric position in the lymphoid follicles. These findings closely agree with the present study.

Radhika D et al., state that lymphoid aggregation begins at the 11<sup>th</sup> week; in the present study, diffuse lymphoid aggregation begins at the 18<sup>th</sup> week [19]. The lymphoid follicles start to develop by the 20<sup>th</sup> week of gestation. A well-demarcated follicle with a centrally placed arteriole was observed at the 32<sup>nd</sup> week; in the present study, a well-defined lymphoid follicle with a central arteriole was observed at the 30<sup>th</sup> week. The matured lymphoid follicle with eccentrically placed arterioles was noted at the 36<sup>th</sup> week. This study is nearly related to the present study.

Potter EL and Craig JM state that during the first and second trimesters, the foetal spleen consists of few lymphocytes, but perivascular lymphoid aggregation was not seen [20]. In the third trimester, WP consists of lymphoid follicles with a central arteriole. In the present study, lymphocytes, perivascular lymphoid aggregation, and lymphoid follicles appeared in the second trimester by the 14<sup>th</sup> week. These study findings do not correlate with the current study. WP findings of the present are compared with the past literature [Table/Fig-11] [12,13,15-19].

Name of the study	Year	Sample size	Lymphoid aggregation starts at	PALS observed at	Definite White Pulp (WP) noted at
Radhika D et al., [19]	2012	50	11 <sup>th</sup> wk	22 wk	36 wk
Souza AD et al., [18]	2015	15	13-24 wk	20 wk	36 wk
Mukhia R et al., [12]	2016	50	17 wk	20 wk	38 wk
Kunde A [13]	2018	30	20 wk	22 wk	38 wk
Srivani D and Pillai JJ [15]	2019	40	16-20 wk	25-32 wk	33-40 wk
Yatagiri SV et al., [16]	2019	50	17 wk	20 wk	36-40 wk
Thomas S et al., [17]	2019	34	20 wk	24 wk	37-40 wk
Present study	2024	50	22-24 wk	24 wk	36 wk

**[Table/Fig-11]:** A comparison of studies on White Pulp (WP) [12,13,15-19].

### Limitation(s)

The limitation of the present study is, it is not focussed on the gross structures of the spleen.

### CONCLUSION(S)

The present study was conducted to observe the histogenesis in the WP of the human foetal spleen. Detailed knowledge about the histogenesis of the spleen is essential for anatomists and pathologists studying individual variations. In the gestational age group of 36-40 weeks, the WP reaches full development and attains high vascularity. Therefore, the authors may consider using the foetal spleen for transplantation after 36 weeks, as the chances of graft rejection will be reduced. Further research should be directed at the molecular level to elucidate the role of the spleen in immunity and autoimmunity.

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- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

#### PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Jul 27, 2024
- Manual Googling: Nov 09, 2024
- iThenticate Software: Dec 03, 2024 (11%)

#### ETYMOLOGY: Author Origin

#### EMENDATIONS: 7

Date of Submission: **Jul 27, 2024**  
Date of Peer Review: **Sep 30, 2024**  
Date of Acceptance: **Dec 04, 2024**  
Date of Publishing: **Jan 01, 2025**