Review article

The immune cell profile of human fallopian tubes in health and benign pathology: a systematic review

Charlotte H. Rigby [a,1], Fatima Aljassim [a,1], Simon G. Powell [a], James N.R. Wyatt [a], Christopher J. Hill [a,2,*], Dharani K. Hapangama [a,b,2]

[a] Department of Women's and Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool, member of Liverpool Health Partners, Liverpool L8 7SS, UK
[b] Liverpool Women's Hospital NHS Foundation Trust, member of Liverpool Health Partners, Liverpool L8 7SS, UK

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ABSTRACT

The fallopian tubes (FT) play a key role in fertility by facilitating the movement of gametes to promote fertilisation and, subsequently, passage of the zygote for implantation. Histologically, the FT mucosa consists of three main cell types: secretory, ciliated and peg cells. In addition, several studies have reported the presence of immune cells. This systematic review aims to present a comprehensive analysis of the immune cell populations in the human FT, both in health and benign pathology, to promote a better understanding of tubal pathologies and their influence on infertility. A comprehensive literature search was conducted across five databases and augmented with manual citation chaining. Forty-two eligible studies were selected in accordance with PRISMA guidelines. Following screening, risk of bias assessments were conducted, data extracted and the findings presented thematically. T lymphocytes, predominantly CD8^{+} T cells, represent the most abundant immune cell population within the healthy FT, with B lymphocytes, macrophages, NK cells and dendritic cells also localised to the tubal mucosa. There is evidence to suggest that lymphocyte and macrophage populations are susceptible to changes in the concentration of reproductive hormones. Tubal ectopic pregnancy, salpingitis, hydrosalpinx and endometriosis are all characterised by an increased population of macrophages in comparison to healthy FT. However, given the inconsistent evidence presented between studies, and the lack of studies examining all immune cell subtypes in tubal pathologies, only limited conclusions can be formulated on pathology-specific immune cell populations, and further research is required for validation.

1. Introduction

The fallopian tubes (FT) are a pair of hollow, seromuscular organs that form part of the female reproductive system. Originating from the uterine horns and projecting laterally within the broad ligament, they extend towards the ovaries (Han and Sadiq, 2022). The tubes are divided anatomically into four regions: uterine, isthmic, ampullary and infundibulum. The infundibulum terminates in ciliated projections, termed fimbriae, which surround the ovaries (Briceag et al., 2015; Vang and Wheeler, 2011). By providing a connection between the ovaries and uterus, the FT play a key role in fertility, facilitating the movement of gametes to promote fertilisation and subsequent passage of the zygote

for implantation (Croxatto, 2002). Consequently, the development of tubal disease has been reported to account for up to 35% of infertility cases (Serafini and Batzofin, 1989).

Pelvic inflammatory disease (PID), an infection of the upper genital tract, is known to induce varying sequelae within the FT, namely salpingitis, hydrosalpinx and pyosalpinx (Vang and Wheeler, 2011). Salpingitis describes inflammation of the FT (Vang and Wheeler, 2011), while hydrosalpinx and pyosalpinx, both resulting from tubal obstruction, refer to distension of the tubal lumen following accumulation of fluid and purulent exudate, respectively (Vang and Wheeler, 2011). Ectopic pregnancies, where the embryo is implanted outside of the uterine cavity, occur in up to 2% of all pregnancies and over 95% of

these are located in the FT (Breen, 1970; Vang and Wheeler, 2011). PID is also an important risk factor for ectopic pregnancy, and maternal death resulting from ectopic pregnancy creates a significant burden for the health service worldwide (Marion and Meeks, 2012). Endometriosis, a chronic inflammatory disease characterised by the development of ectopic endometrial tissue, also commonly implicates the FT and is thought to contribute to tubal cause of infertility (Hill et al., 2020).

Histologically, the external serosa, intermediate muscularis and internal mucosa represent the three layers of the FT (Vang and Wheeler, 2011) (Fig. 1). The mucosa, consisting of luminal epithelium and underlying lamina propria, is predominantly comprised of three main cell types: ciliated, secretory and peg cells (Vang and Wheeler, 2011) (Fig. 1). Basally-located peg cells have been proposed as the stem/progenitor cells responsible for regeneration of the endosalpinx (Paik et al., 2012). There is evidence to suggest that tubal epithelium experiences a low degree of proliferative activity related to the oestrogen-dominant preovulatory menstrual phase (George et al., 2012; Maclean et al., 2020). Through expression of both oestrogen and progesterone receptors, tubal epithelial cells have been identified to exhibit characteristic changes during the course of the menstrual cycle (Donnez et al., 1985; Maclean et al., 2020). Most notably, high serum oestrogen has been linked to increased epithelial height, ciliation, and mitotic activity, whilst progesterone elicits an opposing response (Donnez et al., 1985). In addition to epithelial cells, several studies have also reported a population of immune cells within the FT from both innate and adaptive responses (Lee et al., 2015; Vang and Wheeler, 2011; Wira et al., 2005). Characterisation of this population could be vital in promoting a better understanding of tubal pathologies and their influence on infertility, leading to improvements in women's sexual and reproductive health.

The aim of this systematic review, through identification and appraisal of existing literature, is to present a comprehensive analysis of the immune cell populations in the human FT, both in health and benign pathology.

2. Methods

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Page et al., 2021) and was preceded by a prospectively written protocol, registered with PROSPERO (registration number: CRD42021288257) (Aljassim et al., 2021).

2.1. Search strategy and selection criteria

A comprehensive search of the literature was conducted from inception to April 2022. The NICE Healthcare Databases Advanced Search (HDAS) platform using CINAHL, EMBASE and EMCARE, in addition to Scopus and PubMed, were searched for relevant published material. The search strategy included the following Medical Subject Heading (MeSH) terms, keywords, and their combinations: (Leukocyte or Leucocyte or Macrophage or Neutrophil or Lymphocyte or "NK cell" or "Natural killer cell" or Monocyte or Eosinophil or Basophil or "T cell" or "B cell" or "Immune cell" or "White blood cell") and ("Fallopian tube" or Oviduct or "Uterine tube"). No filters were applied to the search, and an asterisk was used as a wildcard symbol to encompass various word endings where necessary. To avoid the omission of potentially eligible studies, database searches were augmented with manual forward and backward citation chaining, and additional literature was identified through the 'Similar articles' feature on PubMed.

Search results were uploaded into Rayyan, an electronic systematic review software for screening titles and abstracts. Two independent reviewers removed duplicated literature (Ouzzani et al., 2016) and performed a title and abstract screen according to the inclusion and exclusion criteria. The studies meeting the following criteria were included: (1) concerning the immune cell population of human FT in health or benign pathology; (2) population of pre-menopausal, pregnant and/or post-menopausal women; (3) publications in the English language. The exclusion criteria were as follows: (1) exclusive focus on malignant pathology; (2) animal studies; (3) secondary, non-electronic and grey literature. Following retrieval, full-text reviews were conducted by two independent reviewers. A third reviewer was consulted for the resolution of any disagreements.

2.2. Data extraction and analysis

Data from all eligible studies were extracted and recorded into a standardised Excel spreadsheet recording the following: first author, year of publication, study aim, sample size with comparator groups, experimental methods, cell types identified (including antibodies used for immunohistochemistry, where applicable), relevant results and author conclusions. For the purpose of data analysis, eligible studies were categorised into different themes based on; (1) menopausal status and/or cycle phase of the study population; (2) health of FT; (3) type of immune cells. Given the heterogeneity of both methods and results, statistical meta-analysis was not feasible. Consequently, data from the included studies have been thematically synthesised. Two reviewers independently identified recurring themes in included studies, and individual study results were compared with reference to their quality and the conclusions drawn.
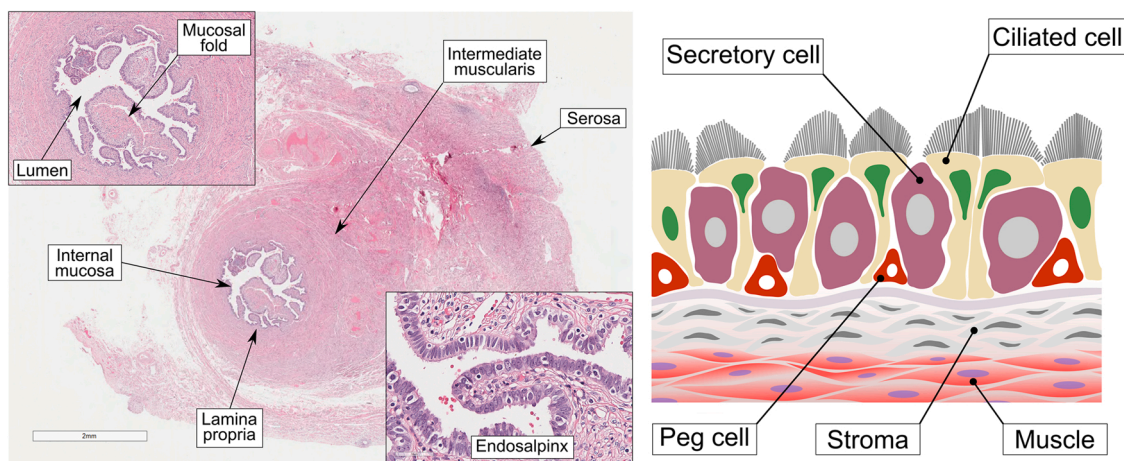
Fig. 1. Fallopian tube anatomy. Haemotoxylin and eosin stained transverse section of the fallopian tube highlighting anatomical structures. The endosalpinx is composed of secretory, ciliated and peg cells that overlay the basement membrane and lamina propria.

2.3. Quality assessment

The risk of bias assessment was performed using two established tools by two independent reviewers. For case-control and cohort studies, the Newcastle-Ottawa scale (NOS) was used (Wells et al., 2021), which evaluates each study based on three broad domains: selection, comparability and outcome. Following the guidelines provided by the NOS, each study receives a score between 0 and 9, which categorises as either good, fair or poor.

For case series and case reports, a modified version of the NOS proposed by Murad et al. (2018) was used, consisting of eight questions across four domains: selection, ascertainment, causality, and reporting. Though a formal score of 0 – 8 can be attributed to each study based on binary responses to each question, a numerical representation of methodological quality is not always recommended when certain questions are deemed more critical than others. Therefore, an overall judgement of methodological quality for each paper was made based on questions 1, 2, 3, 4, 6, and 8. The risk of bias assessment is shown in Table 1 and Table 2.

3. Results

The predefined search strategy identified 4416 publications, of which 2596 remained after duplicate removal. Eligibility screening of these publications, based on the assessment of their title and abstract following the predetermined inclusion and exclusion criteria, led to the exclusion of a further 2427 publications. The remaining 169 full-text articles were sought for retrieval where, following evaluation, an additional 128 articles were excluded. Subsequently, 42 studies are included in the present review. A PRISMA flow diagram of the selection process is shown in Fig. 2 (Page et al., 2021). Table 3 provides a summary of the studies included in this systematic review.

3.1. Immune cell populations in the healthy fallopian tube

T lymphocytes represent the dominant immune cell population in the healthy FT, as identified primarily by immunohistochemistry (IHC) and flow cytometry in 17 studies (Ardighieri et al., 2014; Boehme and Donat, 1992; Dinh et al., 2021; Edelstam and Karlsson-Parra, 1996; Givan et al., 1997; Kutteh et al., 1990; Morris et al., 1986; Mselle et al., 2007; Pröll et al., 2000; Rabi et al., 2014a; Ramraj et al., 2018; Shaw et al., 2011; Ulziibat et al., 2006; Varga et al., 2019; Von Rango et al., 2001; Wicherek et al., 2008; Wollen et al., 1994). Studies have also shown them to account for approximately 40 – 60% of all leucocytes (Mselle et al., 2007; Wollen et al., 1994) and are predominantly localised as rows of single cells within the epithelium, along the basement membrane (Ardighieri et al., 2014; Varga et al., 2019; Wollen et al., 1994). Among T lymphocytes, CD8$^+$ suppressor/cytotoxic T cells were consistently the most abundant subset (Ardighieri et al., 2014; Boehme and Donat, 1992; Dinh et al., 2021; Morris et al., 1986; Pröll et al., 2000; Shaw et al., 2011; Wollen et al., 1994), though one study recorded CD4$^+$ helper T cells as more populous (Kutteh et al., 1990). Generally, CD8$^+$ T cells were located within the epithelium (Ardighieri et al., 2014; Edelstam and Karlsson-Parra, 1996; Wollen et al., 1994), although they were also observed intraepithelially and in the lamina propria (Wollen et al., 1994). CD4$^+$ T-helper cells were more scarcely distributed and sometimes absent, though when present, most often localised within the lamina propria (Ardighieri et al., 2014; Boehme and Donat, 1992; Dinh et al., 2021; Edelstam and Karlsson-Parra, 1996; Morris et al., 1986; Rabi et al., 2014a; Shaw et al., 2011; Ulziibat et al., 2006; Varga et al., 2019; Wollen et al., 1994). B lymphocytes represented a smaller proportion of leucocytes in the FT, constituting between 5% and 10% (Givan et al., 1997; Wollen et al., 1994), also predominantly within the lamina propria (Ardighieri et al., 2014; Wollen et al., 1994). Two studies were not able to detect any B lymphocytes (Morris et al., 1986; Ulziibat et al., 2006).

The reported population of innate immune cells within the healthy FT is inconsistent between studies. Macrophages have been identified in thirteen studies using a combination of histochemical staining and flow cytometry (Ardighieri et al., 2014; Copperman et al., 2006; Dinh et al., 2021; El-Din Safwat et al., 2008; Gaytán et al., 2007; Givan et al., 1997; Haney et al., 1983; Matsushima et al., 2002; Morris et al., 1986; Ramraj et al., 2018; Suenaga et al., 1998; Von Rango et al., 2001; Wang et al., 2020) though their distribution reported to range from the predominant immune cell (Ramraj et al., 2018) to complete absence (Varga et al., 2019). Gaytán et al. (2007) documented their location as primarily within the epithelium and connective tissue of the lamina propria. Langerhans cells, a type of tissue-resident macrophage, were also reportedly localised in the epithelium and lamina propria (Ardighieri et al., 2014; Hagiwara et al., 1998; Rabi et al., 2014a). They were identified by IHC and electron microscopy in five studies as scantily distributed (Ardighieri et al., 2014; Hagiwara et al., 1998; Pröll et al., 2000; Rabi et al., 2014a, 2014b), with Hagiwara et al. (1998) detecting the cells in only 44% of their samples.

Table 1

Risk of bias assessment. Case series and case reports scored using the tool proposed by Murad et al. (2018).

Author Year	Selection	Ascertainment		Causality				Reporting	Total	
	1	2	3	4	5	6	7	8		
Ardighieri et al. (2014)			★	★		★	–	★	4	Fair
Boehme and Donat (1992)			★	★		★	–		3	Poor
Crow et al. (1994)	★		★	★		★	–	★	5	Good
Dinh et al. (2021)			★			★	–	★	3	Fair
El-Din Safwat et al. (2008)	★		★	★		★	–	★	5	Good
Gaytán et al. (2007)	★		★	★		★	–	★	5	Good
Givan et al. (1997)			★	★		★	–	★	4	Fair
Gray and Libbey (2001)	★		★	★		★	–	★	5	Good
Hagiwara et al. (1998)			★				–	★	2	Poor
Idrees et al. (2007)	★		★	★		★	–	★	5	Good
Morris et al. (1986)	★		★	★			–	★	4	Fair
Mselle et al. (2007)			★			★	–	★	3	Fair
Rabi et al. (2014a)			★			★	–	★	3	Fair
Rabi et al. (2014b)			★	★		★	–	★	4	Fair
Ramraj et al. (2018)	★		★			★	–	★	4	Fair
Suárez-Vilela et al. (2011)		★	★	★		★	–	★	5	Good
Suenaga et al. (1998)		★	★	★		★	–	★	5	Good
Varga et al. (2019)			★	★			–	★	3	Fair
Wollen et al. (1994)			★	★		★	–	★	4	Fair
Zhang et al. (2012)		★	★	★		★	–		4	Fair
Zorzi et al. (2010)		★		★			–		2	Poor

Table 2

Risk of bias assessment. Cohort and case-control studies scored using the Newcastle-Ottowa scale (Wells et al., 2021).

Cohort studies

| Author Year	Selection				Comparability		Outcome			Total	
	1	2	3	4	5	6	7	8	9		
Copperman et al. (2006)	★	★		★	★	★	★	★	★	8	Good
Earl et al. (1987)					★			★		2	Poor
Edelstam and Karlsson-Parra (1996)					★	★		★	★	4	Poor
Geppert et al. (1977)					★			★	★	3	Poor
Haney et al. (1983)	★			★	★	★	★	★	★	7	Fair
Kutteh et al. (1990)	★			★	★		★		★	5	Fair
Matsushima et al. (2002)	★	★		★	★	★		★	★	7	Good
Pröll et al. (2000)	★				★		★	★	★	5	Poor
Shaw et al. (2011)	★			★	★		★		★	5	Fair
Ulziibat et al. (2006)					★	★	★	★	★	5	Poor
Von Rango et al. (2001)	★				★	★	★	★	★	6	Poor
Wang et al. (2020)	★	★		★	★	★	★	★	★	8	Good
Wicherek et al. (2008)	★	★		★	★		★	★	★	7	Good
Case-control studies											
Kemp et al. (2007)	★		★	★	★		★	★	★	7	Good
Kemp et al. (2011)	★		★	★	★	★	★	★	★	8	Good
Kinnunen et al. (2000)	★			★			★	★	★	5	Poor
Laskarin et al. (2010)			★		★		★	★	★	5	Poor
Marx et al. (1999)			★	★	★		★	★	★	6	Fair
Ordi et al. (2006)		★	★		★		★	★	★	6	Fair
Vassiliadou and Bulmer (1998)	★			★	★		★	★	★	6	Fair
Wicherek et al. (2006)	★		★	★	★	★	★	★	★	8	Good
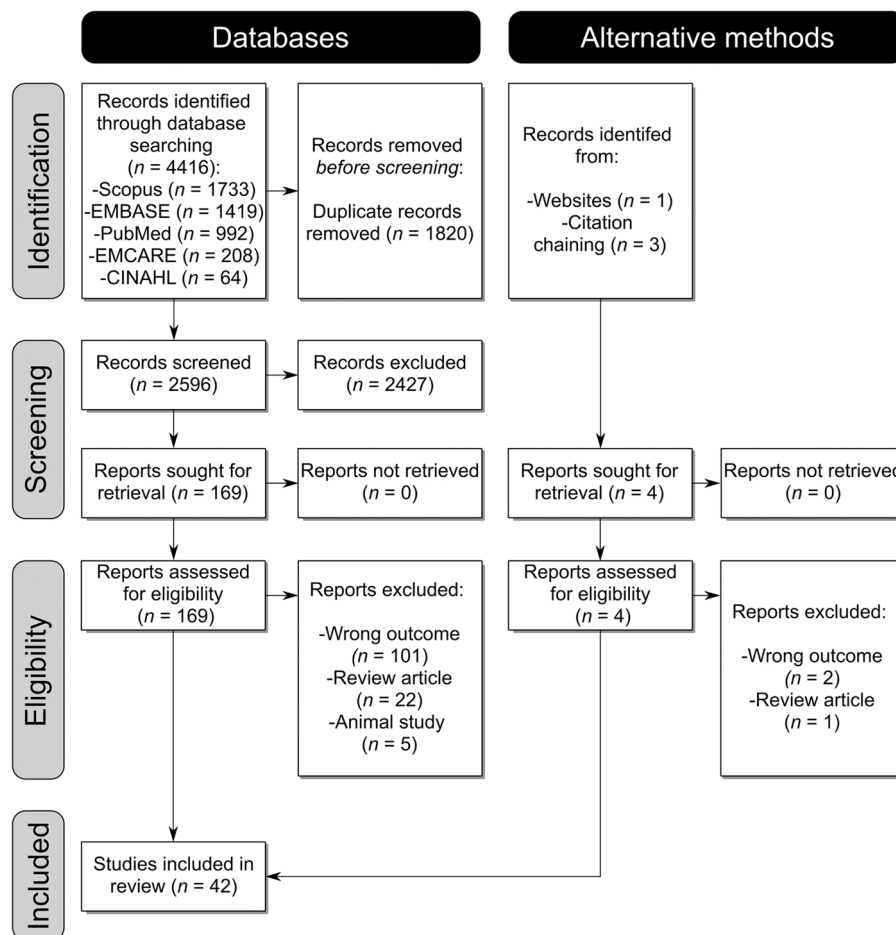
Fig. 2. PRISMA flow diagram presenting the selection process for studies included in this systematic review (Page et al., 2021).

Natural killer (NK) cells, mainly identified via CD16 and CD56 expression, had varying reports of distribution in the healthy FT. Despite an absence of NK cells reported in three studies (Varga et al., 2019; Von Rango et al., 2001; Wicherek et al., 2008), Shaw et al. (2011) found a population of CD56^{dim}CD^{16-} NK cells to represent approximately 10% of all tubal immune cells. Other authors also identified NK cells, though to

Table 3
Summary of studies that assessed the immune cell population of the human fallopian tubes in health and/or benign pathology.

First Author	Title	Method	Immune Cells/ Markers Identified	Relevant Results
Ardighieri et al. (2014)	Characterization of the Immune Cell Repertoire in the Normal Fallopian Tube	IHC, Flow cytometry	CD3, CD4, CD8, CD11c, CD20, CD45, CD56, CD66, CD68, CD117, CD123, CD138, CD163, CD207, CD303 and CD2AP	The predominant immune cells observed in the FT are CD163$^+$ macrophages, CD8$^+$ T lymphocytes and CD11c$^+$ dendritic cells. Additionally, Langerhans cells, CD20$^+$ B lymphocytes, CD56$^+$ NK cells and CD4$^+$ T lymphocytes are present, though less populous.
Boehme and Donat (1992)	Identification of Lymphocyte Subsets in the Human Fallopian tube	IHC	CD3, CD4, CD8 and CD22	CD3$^+$ and CD8$^+$ T lymphocytes are the main immune cells in the FT mucosa, both of which are more prevalent in the proliferative phase than the secretory phase of the menstrual cycle. B lymphocytes and T-helper lymphocytes also present, but less frequent.
Copperman et al. (2006)	Presence of hydrosalpinx correlated to endometrial inflammatory response in vivo	Histochemical staining	Neutrophils, lymphocytes, plasma cells, eosinophils, basophils and macrophages	Cases of hydrosalpinx have a significant increase in the number of immune cells, including neutrophils, lymphocytes, plasma cells, and macrophages, compared to age-matched controls with normal tubal architecture
Crow et al. (1994)	Morphology and ultrastructure of fallopian tube epithelium at different stages of the menstrual cycle and menopause	Light microscopy, Electron microscopy	Lymphocytes	Intra-epithelial lymphocytes observed; their population does not vary between menstrual phases. However, greater numbers of lymphocytes were detected in postmenopausal cases.
Dinh et al. (2021)	Single-cell transcriptomics identifies gene expression networks driving differentiation and tumorigenesis in the human fallopian tube	IHC, Flow cytometry, single-cell transcriptomics	CD4, CD8, B cells, dendritic cells, fibroblasts, macrophages, mast cells, monocytes, NK cells and plasma cells	The immune cell population of the healthy FT is dominated by T lymphocytes, of both CD4$^+$ and CD8$^+$ phenotype, and NK cells. Other immune cells such as macrophages, mast cells, monocytes, dendritic cells, and B lymphocytes were less prevalent.
Earl et al. (1987)	Leucocyte populations in ectopic tubal pregnancy	IHC	CD2, CD3, CD5, CD7, CD8, CD22, tissue macrophages and granulocytes	Both lymphocytes and histiocytes were detected at the tubal implantation site, whilst plasma cells were scarce. Leucocytes were present in all samples, mostly macrophages but also T lymphocytes, B lymphocytes, monocytes and granulocytes detected.
Edelstam and Karlsson-Parra (1996)	The human leucocyte antigen (HLA) DR expression and the distribution of T-Lymphocytes in the fimbriae of the normal fallopian tube and during pelvic adhesion disease	IHC	CD3, CD4 and CD8	CD3$^+$ T lymphocytes were moderately distributed in healthy FT fimbriae, with both CD4$^+$ and CD8$^+$ cells detected. In cases of hydrosalpinx, an increased number of T lymphocytes were identified, mainly localised to the lamina propria and of CD4$^+$ phenotype.
El-Din Safwat et al. (2008)	Distribution of macrophages in the human fallopian tubes: an immunohistochemical and electron microscope study	IHC, Electron microscopy	CD68	The number of CD68$^+$ cells in healthy FT were significantly decreased in postmenopausal samples compared to premenopausal samples. The population of CD68$^+$ cells also fluctuate during the menstrual cycle. These cells were much more frequently detected in the secretory phase compared to the proliferative phase.
Gaytán et al. (2007)	Macrophages in human fallopian tube and ovarian epithelial inclusion cysts	IHC	CD68, CD163 and Mac387	Macrophages in the FT are localised to the epithelium and lamina propria. They show cyclical changes, particularly in the epithelium where they are more populous in the early-mid luteal phase.
Geppert et al. (1977)	On the Lympho-Epithelial Relationships in the Human Oviduct	Histochemical staining, Electron microscopy	Lymphocytes	The lymphocyte population of the FT is variable. The number of lymphocytes in the epithelium is significantly increased during the secretory phase, compared to the proliferative phase. Similarly, they are significantly more prevalent in premenopausal samples than postmenopausal samples. Cases of pyosalpinx and tubal ectopic pregnancy do not affect the number of lymphocytes.
Givan et al. (1997)	Flow cytometric analysis of leukocytes in the human female reproductive tract: Comparison in fallopian tube, uterus, cervix and vagina	Histochemical staining, Flow cytometry	CD3, CD14, CD19, CD45 and CD66	Leucocytes were identified in the FT, they included T lymphocytes, granulocytes, monocytes/macrophages, and B cells. These leucocytes did not show variations during the menstrual cycle or between pre- and postmenopausal samples.
Gray and Libbey (2001)	Xanthogranulomatous salpingitis and oophoritis: A case report and review of the literature	Histochemical staining	Histiocytes, lymphocytes, plasma cells and neutrophils	One case of haemosiderin-laden histiocyte infiltration of the lamina propria, accompanied by neutrophils, lymphocytes, and plasma cells. This case was associated with previous PID

Table 3 (*continued*)

First Author	Title	Method	Immune Cells/ Markers Identified	Relevant Results
				following intrauterine device insertion and termed "xanthogranulomatous salpingitis".
Hagiwara et al. (1998)	Langerhans cells in the human oviduct mucosa	IHC, Electron microscopy	CD1a	CD1a Langerhans cells identified in the epithelium and lamina propria of the healthy FT. Though only detected in 44% of samples, the Langerhans cells were most densely distributed in patients aged between 46 and 52.
Haney et al. (1983)	Macrophages and infertility: Oviductal macrophages as potential mediators of infertility	Histochemical staining	Macrophages	The highest number of oviductal macrophages was found in patients with endometriosis, whilst patients with oviductal obstruction had the fewest.
Idrees et al. (2007)	Xanthogranulomatous salpingitis associated with fallopian tube mucosal endometriosis: a clue to the pathogenesis	IHC	CD45 and CD68	One case, associated with extensive FT endometriosis, histologically presented with tubal plicae dilation by foamy ceroid-laden macrophages. Accompanied by numerous inflammatory cells, mainly lymphocytes, plasma cells and mast cells.
Kemp et al. (2007)	Tubal abortions but not viable tubal pregnancies are characterized by an increased number of CD8 + T cells	IHC	CD3, CD8, CD20, CD45 and CD68	There were significantly higher numbers of leucocytes detected at the implantation site of non-live tubal pregnancies compared to live tubal pregnancies. With numbers of $CD3^+$, $CD8^+$, $CD20^+$ and $CD68^+$ cells all significantly higher in non-live tubal pregnancies.
Kemp et al. (2011)	Dendritic cells are equally distributed in intrauterine and tubal ectopic pregnancies	IHC	CD14, CD83, DEC205 and DC-SIGN	Viable tubal pregnancies have low numbers of $CD83^+$ and $DEC205^+$ mature dendritic cells. However, a large number of DC-SIGN$^+$ immature dendritic cells were observed, and, of these, approximately two-thirds expressed $CD14^+$.
Kinnunen et al. (2000)	Chlamydia trachomatis reactive T lymphocytes from upper genital tract tissue specimens	IHC	CD4, CD8, CD15, CD20, CD25 and CD45RO	$CD4^+$, $CD8^+$, $CD15^+$, $CD20^+$ and $CD45RO^+$ cells were all detected in cases of hydrosalpinx. $CD4^+$ cells were more frequently detected than $CD8^+$ cells.
Kutteh et al. (1990)	Secretory immune system of the female reproductive tract. II. Local immune system in normal and infected fallopian tube	IHC	Plasma cells, T lymphocytes, T-helper/inducer lymphocytes, T-suppressor/cytotoxic lymphocytes and NK cells	In the healthy FT, T lymphocytes were detected, with $CD4^+$ T cells accounting for 67% of all T lymphocytes. $CD8^+$ T cells were present but less frequently. NK cells were also detected, but in low numbers. Ig-positive plasma cells were observed in healthy FT, and in cases of salpingitis where they were significantly increased.
Laskarin et al. (2010)	Phenotype of NK Cells and Cytotoxic/ Apoptotic Mediators Expression in Ectopic Pregnancy	IHC, Flow cytometry	CD3, CD16, CD56, CD94 and NKG2A	$CD56^+$ cells account for 6.53% of all leucocytes at the tubal implantation site in ectopic pregnancy, compared to 14.5% in the tubal mucosa distant to the implantation site.
Marx et al. (1999)	Leukocyte populations, hormone receptors and apoptosis in eutopic and ectopic first trimester human pregnancies	IHC	CD3, CD8, CD56 and CD68	In tubal ectopic pregnancy, the immune cell population of the tubal epithelium is characterised by mainly $CD3^+$ and $CD68^+$ cells. No $CD56^+$ cells were detected.
Matsushima et al. (2002)	Assessment of Fallopian Tube Cytology for the Diagnosis of Endometriosis and Hydrosalpinx	Histochemical staining	Macrophages, neutrophils, monocytes and lymphocytes	In the healthy FT, few inflammatory cells observed. In cases of pelvic endometriosis, macrophages were very prevalent in various morphological states e.g., foamy cells. In cases of hydrosalpinx, though only few cells could be obtained, most were inflammatory, including monocytes, lymphocytes, and neutrophils.
Morris et al. (1986)	Lymphoid tissue of the normal fallopian tube-a form of mucosal-associated lymphoid tissue (MALT)?	IHC, Electron microscopy	T lymphocytes, B lymphocytes, T-helper lymphocytes, T-cytotoxic/suppressor lymphocytes, monocytes, macrophages and NK cells	In the healthy FT, intraepithelial lymphocytes were frequently detected, mainly located basally. These were predominantly cytotoxic/ suppressor T lymphocytes, though macrophages and B lymphocytes were also detected.
Mselle et al. (2007)	Unique characteristics of NK cells throughout the human female reproductive tract	Flow cytometry	CD3, CD9, CD16, CD45, CD56, CD69 and CD94	NK cells account for 6% of all leucocytes in the healthy FT. The number of leucocytes present in the FT is decreased in those aged over 60, and consequently the percent of NK cells is significantly reduced in those aged over 60 compared to those aged under 60.
Ordi et al. (2006)	Uterine (CD56 +) Natural Killer Cells Recruitment: Association with Decidual Reaction Rather than Embryo Implantation	IHC	CD3, CD4, CD8, CD16, CD20, CD56, CD57 and CD68	$CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$, $CD57^+$ and $CD68^+$ cells were detected in all samples of tubal ectopic pregnancy. However, $CD20^+$ cells and $CD56^+$ cells were only present in between 65% and 70% of samples.
Pröll et al. (2000)	Tubal versus uterine placentation: similar HLA-G expressing extravillous cytotrophoblast	IHC		$CD1a^+$, $CD1b^+$, $CD1c^+$ and $CD8^+$ cells were located in the tubal mucosa of tubal ectopic

Table 3 (*continued*)

First Author	Title	Method	Immune Cells/ Markers Identified	Relevant Results
	invasion but different maternal leukocyte recruitment		CD1a, CD1b, CD1c, CD4, CD8, CD14, CD16, CD20, CD25, CD56, CD83 and HLA-DR	pregnancies. In addition, CD4$^+$, CD14$^+$, CD16$^+$ and CD83$^+$ cells were detected, but less frequently. However, no CD56$^+$, CD20$^+$ or CD25$^+$ cells were identified.
Rabi et al. (2014a)	Different subsets of Langerhans cells in human uterine tubes and uterus	IHC	CD1a, CD4, CD8 and ZIO	CD1a$^+$ cells were scarcely distributed in the epithelium and lamina propria of healthy FT, whilst ZIO$^+$ Langerhans cells were present in significantly greater numbers. CD4$^+$ and CD8$^+$ cells were also present, but few in number.
Rabi et al. (2014b)	Ultrastructural demonstration of antigen presenting cells in human uterine tube	IHC, Electron microscopy	Dendritic cells, lymphocytes and Langerhans cells	Intraepithelial lymphocytes and Langerhans cells were located in the epithelium of healthy FT, whilst dendritic cells were observed in the lamina propria.
Ramraj et al. (2018)	Correlation of clinical data with fallopian tube specimen immune cells and tissue culture capacity	Flow cytometry	CD4, CD8, CD16, CD25, CD56 and CD68	Fimbriae specimens from healthy FT were predominated by M1 macrophages, accounting for 20% of all cells. T-regulatory cells, CD8$^+$ cytotoxic T cells, M2 macrophages and NK cells were also localised.
Shaw et al. (2011)	Lymphoid and myeloid cell populations in the non-pregnant human Fallopian tube and in ectopic pregnancy	Flow Cytometry, IHC	CD3, CD4, CD8, CD11c, CD14, CD16, CD45, CD56 and CD68	Immune cells detected in the healthy FT include CD3$^+$ cells, with CD8$^+$ more populous than CD4$^+$, monocytes, dendritic cells, neutrophils, and NK cells. CD123$^+$ dendritic cells were more common than CD11c$^+$. However, the number of CD11c$^+$ cells were significantly increased in the luteal phase compared to the follicular phase of the menstrual cycle. In tubal ectopic pregnancy, the numbers of CD68$^+$, CD11c$^+$ and CD45$^+$ were significantly increased compared to healthy FT tissue
Suárez-Vilela et al. (2011)	Pseudoxanthomatous salpingitis: Report of two cases with distinctive microscopical findings	IHC	CD3, CD4, CD8, CD10, CD20, CD34, CD43 and CD68	Two cases of pseudoxanthomatous salpingitis. One characterised by tubal plicae expansion with pigmented histiocytes, some lymphocytes also identified. The other with extensive histiocyte infiltration of the lamina propria, mostly pigmented.
Suenaga et al. (1998)	Distribution and cytological properties of macrophages in human fallopian tubes	IHC, Electron microscopy	PM-K1 and PM-K2	PM-K1$^+$ cells (CD68 macrophages) and PM-K2$^+$ cells (tissue resident macrophages) were detected in the healthy FT mucosa. In the early and mid-secretory phases of the menstrual cycle, the number of PM-K1$^+$ cells were significantly increased in comparison to the proliferative phase. Conversely, the population of PM-K2$^+$ cells is small, and relatively constant through the menstrual cycle.
Ulziibat et al. (2006)	Identification of estrogen receptor β-positive intraepithelial lymphocytes and their possible roles in normal and tubal pregnancy oviducts	IHC	CD3, CD4, CD8 and CD20	All intraepithelial lymphocytes expressed CD8$^+$, however no CD4$^+$ cells or CD20$^+$ cells were detected. The percentage of intraepithelial lymphocytes per total number of epithelial cells was increased during the late secretory and late proliferative phase of the menstrual cycle, and in tubal ectopic pregnancy. However, they were significantly decreased in the early secretory phase, and in post-menopausal specimens.
Varga et al. (2019)	How many cell types form the epithelial lining of the human uterine tubes? Revision of the histological nomenclature of the human tubal epithelium	IHC	CD1a, CD3, CD4, CD8, CD30, CD45RO, CD56 and CD68	CD3$^+$, CD8$^+$ and CD45RO T lymphocytes detected in healthy tubal mucosa. B lymphocytes were also identified, though less prevalent. Macrophages, NK cells and dendritic cells all reported absent.
Vassiliadou and Bulmer (1998)	Characterization of tubal and decidual leukocyte populations in ectopic pregnancy: Evidence that endometrial granulated lymphocytes are absent from the tubal implantation site	IHC	CD3, CD20, CD43, CD45, CD45RA, CD56, CD57 and CD68	In tubal ectopic pregnancy, the most abundant immune cell type at the implantation site was the CD3$^+$ T lymphocytes. Macrophages were the second most populous. NK cells and B cells were present but less frequently detected.
Von Rango et al. (2001)	Effects of trophoblast invasion on the distribution of leukocytes in uterine and tubal implantation sites	IHC	CD8, CD20, CD45, CD56 and CD68	In tubal ectopic pregnancies, the implantation site has a population of CD8$^+$, CD20$^+$, and CD68$^+$ cells. CD68$^+$ macrophages were most frequently detected at the centre of the implantation site, whilst CD20$^+$ B cells were located at the invasion front. CD56$^+$ cells were absent in tubal mucosa. The number of CD45$^+$ leucocytes and CD68$^+$ macrophages in the tubal mucosa of tubal ectopic pregnancies is significantly higher than in the normal tubal mucosa.
Wang et al. (2020)			CD68, CD80, CD163 and CD206	

Table 3 (*continued*)

First Author	Title	Method	Immune Cells/ Markers Identified	Relevant Results
	Adrenomedullin insufficiency alters macrophage activities in fallopian tube: a pathophysiologic explanation of tubal ectopic pregnancy	IHC, Flow cytometry		The number of CD68^{+} macrophages are significantly increased in tubal ectopic pregnancy and salpingitis, compared to healthy FT. The macrophages are spread throughout epithelium and lamina propria and express the M1 phenotype.
Wicherek et al. (2008)	Analysis of metallothionein, RCAS1 immunoreactivity regarding immune cell concentration in the endometrium and tubal mucosa in ectopic pregnancy during the course of tubal rupture	IHC	CD3, CD25, CD56 and CD69	In ruptured tubal ectopic pregnancies, the number of CD3^{+} and CD56^{+} cells were significantly higher than those in unruptured tubal ectopic pregnancies without intraperitoneal bleeding. CD69 antigen expression was similarly increased. CD25^{+} cells were also identified in both ruptured and unruptured tubal ectopic pregnancies, though the number of which were not significantly different. CD3^{+} cells and CD69 expression were observed in the FT tissue of non-pregnant controls, however CD56^{+} and CD25^{+} cells were absent.
Wicherek et al. (2006)	Metallothionein expression and infiltration of cytotoxic lymphocytes in uterine and tubal implantation sites	IHC	CD56 and CD69	In specimens of tubal ectopic pregnancy, CD56^{+} cells were identified in 50% of cases, and CD69 expression confirmed in 55%. However, the number of CD56^{+} cells were significantly higher in women with ruptured ectopic pregnancies compared to unruptured.
Wollen et al. (1994)	In situ characterization of leukocytes in the fallopian tube in women with or without an intrauterine contraceptice device	IHC	CD3, CD4, CD8, CD11b, CD19, CD22, and plasma cells	Lymphocytes, granulocytes, plasma cells and mast cells were identified in the tubal mucosa of the healthy FT. Leucocytes are predominately located in the basal epithelium, with T lymphocytes the most abundant immune cell type constituting for around 60% of all leucocytes. CD8^{+} cells were more prevalent than CD4^{+} cells and B lymphocytes were identified in approximately 50% of samples. Granulocytes and monocytes were also observed, though distributed randomly.
Zhang et al. (2012)	Xanthogranulomatous inflammation of the female genital tract: Report of three cases	IHC	CD3, CD5, CD20, CD68 and CD79a	One case of xanthoma cell infiltration in the FT plicae, causing distension. Lymphocytes, neutrophils, and plasma cells accompanied the lesion, that was diagnosed "xanthogranulomatous salpingitis".
Zorzi et al. (2010)	Melanosis tubae: Histogenesis and appropriate terminology	Histological examination	Macrophages, lymphocytes and plasma cells	Two cases of lipofuscin-laden macrophage deposition in the lamina propria of the FT, both associated with endometriosis. With the lesions described as not inflammatory, the term "melanosis tubae" was proposed.

a lesser degree (Dinh et al., 2021; Kutteh et al., 1990; Mselle et al., 2007). Dendritic cells have been detected in four studies by IHC and flow cytometry (Ardighieri et al., 2014; Dinh et al., 2021; Rabi et al., 2014b; Shaw et al., 2011) and reported as absent in another (Varga et al., 2019). Ardighieri et al. (2014) reported CD11c^{+} dendritic cells (conventional) as a predominant innate cell in the FT, whilst Shaw et al. (2011) found CD123^{+} dendritic cells (plasmacytoid) to be more prevalent. Finally, the presence of granulocytes was reported by several studies (Ardighieri et al., 2014; Copperman et al., 2006; Dinh et al., 2021; Givan et al., 1997; Matsushima et al., 2002; Shaw et al., 2011; Wollen et al., 1994). Primarily located within the lamina propria (Ardighieri et al., 2014; Wollen et al., 1994), neutrophils, mast cells, eosinophils and basophils have been identified to represent a minor population within the FT (Ardighieri et al., 2014; Copperman et al., 2006; Dinh et al., 2021; Givan et al., 1997; Matsushima et al., 2002; Shaw et al., 2011; Wollen et al., 1994).

3.2. Menstrual phase

Several studies investigated fluctuations in immune cells between different menstrual cycle phases; three studies reported no variations between cycle phases (Crow et al., 1994; Givan et al., 1997; Kutteh et al., 1990), yet others noted marked changes. Lymphocyte proportions produced inconsistent results between studies; Geppert et al. (1977) reported a significant increase in lymphocytes during the secretory phase, whilst Ulziibat et al. (2006) observed increased lymphocytes in both the late proliferative and late secretory phase with decreases in the early secretory phase. Another study identified increased pan T cells and T suppressor cells in the proliferative phase, though they could only detect B cells during the secretory phase (Boehme and Donat, 1992). In contrast, three studies examining variations in the number of macrophages reported increased numbers during the secretory phase compared to the proliferative phase (El-Din Safwat et al., 2008; Gaytán et al., 2007; Suenaga et al., 1998), two of which provided data showing a significant increase (El-Din Safwat et al., 2008; Suenaga et al., 1998). In addition, a study conducted by Shaw et al. (2011) identified a significant increase in CD11c^{+} expression during the secretory phase compared to the proliferative phase, a marker associated with macrophages, dendritic cells, and inflammatory monocytes.

3.3. Menopausal status

Studies that compared the immune cell populations in pre and postmenopausal FT also presented conflicting results. Whilst two studies reported a decrease in the number of lymphocytes in postmenopausal women (Geppert et al., 1977; Mselle et al., 2007), several others in

contrast identified an increased population of lymphocytes in post-menopausal tubes (Ardighieri et al., 2014; Crow et al., 1994; Hagiwara et al., 1998). Most notably, Ardighieri et al. (2014) reported significantly increased T-helper and B cell numbers in postmenopausal FT. Interestingly, macrophages were consistently reported to be significantly lower in postmenopausal women (Ardighieri et al., 2014; El-Din Safwat et al., 2008) than in women of reproductive age.

One study investigated the population of Langerhans cells in the FT in particular (Hagiwara et al., 1998). Though not significant, they noted that the densest distribution of Langerhans cells in four samples from women aged 46–52 (Hagiwara et al., 1998). The data collated from these studies provide evidence suggesting menopause-associated variations in the immune cell population of human FT.

3.4. Tubal ectopic pregnancy

CD3$^+$ T cells were identified to be the predominant immune cell at the tubal implantation site by Vassiliadou and Bulmer (1998), which accounted for 61% $\pm$ 5.48% of leucocytes present. CD3 expression was reported by five other studies (Earl et al., 1987; Marx et al., 1999; Ordi et al., 2006; Ulziibat et al., 2006; Wicherek et al., 2008), as was CD8 expression (Marx et al., 1999; Ordi et al., 2006; Shaw et al., 2011; Ulziibat et al., 2006; Von Rango et al., 2001), with CD8$^+$ T cells reported to be densely localised towards the trophoblast invasion front (Von Rango et al., 2001). Conversely, CD4$^+$ T-helper cells were recorded as present in some studies (Ordi et al., 2006; Pröll et al., 2000) and absent in others (Ulziibat et al., 2006), while CD20$^+$ B lymphocytes were rarely detected, if at all (Ordi et al., 2006; Pröll et al., 2000; Ulziibat et al., 2006; Vassiliadou and Bulmer, 1998). A study by Ulziibat et al. (2006) identified an increase in the number of lymphocytes in the tubal epithelium in ectopic pregnancy compared to normal FT, however, Geppert et al. (1977) reported a significant decrease.

The presence of innate immune cells has also been explored. CD68 expression, highly associated with macrophages, was found to be significantly elevated in two studies comparing tubal ectopic pregnancy to non-pregnant control FT (Shaw et al., 2011; Wang et al., 2020). In fact, eight studies (Earl et al., 1987; Marx et al., 1999; Ordi et al., 2006; Pröll et al., 2000; Shaw et al., 2011; Vassiliadou and Bulmer, 1998; Von Rango et al., 2001; Wang et al., 2020) identified macrophages or their associated proteins in the FT during tubal pregnancy. According to Vassiliadou and Bulmer (1998), CD68$^+$ cells accounted for 50% $\pm$ 3.96% of leucocytes at the tubal implantation site, which was noted by other studies as evenly distributed throughout the mucosa and lamina propria (Marx et al., 1999; Wang et al., 2020). Kemp et al. (2011), investigating the dendritic cell population in tubal pregnancies, observed large numbers of immature CD209$^+$ dendritic cells, whilst mature CD83$^+$ dendritic cells were rarely identified, with the latter similarly noted by Pröll et al. (2000). The presence of NK cells was inconsistently reported between studies. Flow cytometric analysis performed by Laskarin et al. (2010) recorded that CD56^{dim} cells accounted for 6.53% of all lymphocytes at the tubal implantation site. Importantly, they demonstrated tubal NK cells to have a distinct phenotype (CD56^{dim}, CD94$^-$ and NKG2A$^-$) compared to decidual uterine NK cells (CD56^{bright}, CD94$^+$ and NKG2A$^+$). NK cells were also identified in both studies by Wicherek et al. (2006, 2008) however, they were reported to be completely absent by three studies (Marx et al., 1999; Pröll et al., 2000; Von Rango et al., 2001). CD57 and CD16, additional markers of NK cells, were also observed by some studies, though in low numbers (Ordi et al., 2006; Pröll et al., 2000; Vassiliadou and Bulmer, 1998), while other studies reported the tubal NK cells to be deficient of CD16 (Laskarin et al., 2010).

Tubal rupture, a potentially fatal complication in ectopic pregnancy, was studied by Wicherek et al. in two studies (Wicherek et al., 2006; Wicherek et al., 2008). They noted a significant increase in the number of CD56$^+$ and CD3$^+$ cells in cases of tubal rupture, compared to cases of unruptured ectopic pregnancy without intraperitoneal haemorrhage (Wicherek et al., 2006; Wicherek et al., 2008). Furthermore, NK cells express CD69 after activation by different stimuli and ruptured ectopic pregnancies demonstrate significantly higher CD69 staining compared to unruptured ectopic pregnancies. These findings prompted the proposal that elevated numbers of CD56$^+$ cells accompanied by increased immune cell activity could be a causative factor in tubal rupture (Wicherek et al., 2006; Wicherek et al., 2008).

Only one study investigated the impact of viability of pregnancy on immune cell phenotype (Kemp et al., 2007). By comparing live tubal pregnancies and non-viable tubal pregnancies, they identified a significant increase in the number of CD45$^+$ leucocytes, CD68$^+$ macrophages, CD20$^+$ B cells, CD3$^+$ T cells and CD8$^+$ T cells in non-viable tubal pregnancies compared with live tubal pregnancies (Kemp et al., 2007). Additionally, considering the number and pattern of CD3$^+$ and CD8$^+$ T cells present within serial sample sections, Kemp et al. (2007) concluded that CD3$^+$CD8$^+$ T cells were most likely involved in deeper placentation, thus implicating them in the clinical fate of tubal pregnancies.

3.5. Salpingitis, hydrosalpinx and pyosalpinx

Two studies reported the presence of immune cells in FT with salpingitis (Kutteh et al., 1990; Wang et al., 2020). Wang et al. (2020) demonstrated a general spread of macrophages throughout the mucosa and lamina propria with clustering adjacent to blood vessels, which they concluded to indicate a circulatory origin. They also examined isolated macrophages from cases of salpingitis, and showed that salpingitis-associated chemokines induce these macrophages to produce pro-inflammatory and pro-implantation cytokines such as IL-6 and IL-8 (Wang et al., 2020). Furthermore, Wang et al. (2020) reported a significantly increased proportion of CD68$^+$ macrophages, expressing the M1 phenotype. Similarly, Ig-positive plasma cells showed a significant six- to ten-fold increase in salpingitis cases compared to control healthy FT (Kutteh et al., 1990).

Though no other studies focused solely on salpingitis, a study by Copperman et al. (2006) grouped cases of salpingitis with hydrosalpinx, to assess inflammatory cell populations compared to age-matched healthy FT. The analysis of tubal specimens revealed significantly increased numbers of inflammatory cells, most specifically macrophages, lymphocytes, plasma cells and neutrophils, compared with healthy FT (Copperman et al., 2006).

Immune cells in hydrosalpinx was further investigated by several authors (Edelstam and Karlsson-Parra, 1996; Haney et al., 1983; Kinnunen et al., 2000; Matsushima et al., 2002). T lymphocytes were often identified, mainly localised within the lamina propria, and most commonly expressing the CD4$^+$ phenotype, though CD8$^+$ cells, whilst reported, were less abundant (Edelstam and Karlsson-Parra, 1996; Kinnunen et al., 2000). Monocytes, macrophages, B cells and neutrophils were also detected (Haney et al., 1983; Kinnunen et al., 2000; Matsushima et al., 2002), indicating ongoing immunological activity and Edelstam and Karlsson-Parra (1996) suggested them to be a potential explanation for the low fertility associated with hydrosalpinx. Matsushima et al. (2002) observed the thin tubal mucosa and flattened mucosal folds commonly seen in hydrosalpinx to be associated with very few epithelial or immune cells in comparison to healthy FTs. Although these cells were predominately inflammatory cells, their methodology precluded them from concluding on different immune cell populations present in hydrosalpinx.

Geppert et al. (1977) quantified the number of lymphocytes amongst 1000 tubal epithelial cells in pyosalpinx samples, which were almost exclusively located basally. The average number of lymphocytes in pyosalpinx proved not to be significantly different compared to healthy FT.

3.6. Endometriosis

Very few studies have investigated the presence of oviductal immune

cells in samples collected from women with endometriosis, and they have focused only on the macrophage population. A study conducted by Haney et al. (1983) compared the presence, morphology and in vitro functional characteristics of both oviductal and peritoneal macrophages in patients with endometriosis-associated infertility to a healthy fertile population. The morphological and functional characterisation of the tubal macrophages were similar to peritoneal macrophages, but women with endometriosis had significantly increased oviductal macrophages when compared with the control population, and this also positively correlated with the number of peritoneal macrophages (Haney et al., 1983). A similar study by Matsushima et al. (2002) also identified an increased number of macrophages in the FT of women with pelvic endometriosis compared to healthy FT. Through cytological examination, they visualised macrophages in various morphological states, including foam cells and haemosiderin-laden cells (Matsushima et al., 2002).

3.7. Rare tubal pathologies

Several case reports have been published detailing the characteristic histology of a rare group of pathologies affecting the human FT (Gray and Libbey, 2001; Idrees et al., 2007; Suárez-Vilela et al., 2011; Zhang et al., 2012; Zorzi et al., 2010). Such studies have observed tubal mucosa presenting with small bulbous projections, which microscopically correspond to a marked expansion of tubal plicae infiltrated with lipofuscin-laden histiocytes (Gray and Libbey, 2001; Idrees et al., 2007; Suárez-Vilela et al., 2011; Zhang et al., 2012; Zorzi et al., 2010). Multiple terms such as xanthogranulomatous salpingitis (Gray and Libbey, 2001; Idrees et al., 2007; Zhang et al., 2012), melanosis tubae (Zorzi et al., 2010) and pseudoxanthomatous salpingitis (Suárez-Vilela et al., 2011) have been proposed for the described lesion, which is suggested to have a close association with endometriosis and PID. In some cases, there was an absence of other immune cell types (Zorzi et al., 2010), whereas, in others, histiocytes were accompanied by additional inflammatory cells such as lymphocytes and plasma cells (Gray and Libbey, 2001; Idrees et al., 2007; Suárez-Vilela et al., 2011; Zhang et al., 2012). Suárez-Vilela et al. (2011) performed an immunohistochemical analysis that identified an additional lymphoid infiltrate composed mainly of T lymphocytes, though their two cases presented with inconsistent proportions of CD4$^+$ and CD8$^+$ cells.

The pathogenesis of this rare condition is not well understood, and whilst Zorzi et al. (2010) identified the lesions as non-inflammatory, hence proposing "melanosis tubae" as the most appropriate terminology for diagnosis, other authors described chronic inflammation, believing lesions belong to a wide spectrum of changes caused by multiple aetiologies (Gray and Libbey, 2001; Idrees et al., 2007; Suárez-Vilela et al., 2011; Zhang et al., 2012).

4. Discussion

This review aimed to characterise the immune cell population of human FT both in health and benign pathology. Collated literature reported the presence of a diverse range of immune cells from both the innate and adaptive subsystems. However, there are considerable inconsistencies between the findings presented by different authors and the available studies on tubal pathologies are insufficient. Therefore, it is challenging to comprehensively define the tubal immune cell population and only limited conclusions can be drawn.

In the healthy FT, cells pertinent to adaptive immunity represent the most abundant subsystem of immune cells, which is characterised by a predominant T lymphocyte population. These T lymphocytes account for up to 60% of all tubal leucocytes and are generally distributed along the epithelial basement membrane in rows of single cells (Ardighieri et al., 2014; Wollen et al., 1994). CD8$^+$ T cells are more populous than CD4$^+$ T cells in the healthy FT (Ardighieri et al., 2014; Boehme and Donat, 1992; Dinh et al., 2021; Morris et al., 1986; Pröll et al., 2000;

Shaw et al., 2011; Wollen et al., 1994). B lymphocytes, constituting between 5% and 10% of all healthy FT leucocytes (Givan et al., 1997; Wollen et al., 1994), are less frequently detected than T lymphocytes and primarily localise within the lamina propria (Ardighieri et al., 2014; Wollen et al., 1994).

Interpretation of the innate immune cell population presented a greater challenge due to the divergent published literature on their existence. Some studies report macrophages, NK cells and dendritic cells to be localised within the FT mucosa (Ardighieri et al., 2014; Copperman et al., 2006; Dinh et al., 2021; El-Din Safwat et al., 2008; Gaytán et al., 2007; Givan et al., 1997; Hagiwara et al., 1998; Haney et al., 1983; Kutteh et al., 1990; Matsushima et al., 2002; Morris et al., 1986; Mselle et al., 2007; Pröll et al., 2000; Rabi et al., 2014a, 2014b; Ramraj et al., 2018; Shaw et al., 2011; Suenaga et al., 1998; Von Rango et al., 2001; Wang et al., 2020), whilst others report these cells to be absent (Ulziibat et al., 2006; Varga et al., 2019; Wicherek et al., 2008). One possible explanation for these disagreements arises from the inconsistent use of phenotypic markers; there are several different clusters of differentiation (CD) molecules that can be used to detect specific cell types. For example, dendritic cell markers include, but are not limited to, CD1a, CD11c, CD14, CD45RA and CD123 (Collin et al., 2013). Varga et al. (2019) reported an absence of dendritic cells using the CD1a antibody; however, Shaw et al. (2011) described a population of both conventional and plasmacytoid dendritic cells using CD11c and CD123 antibodies. Therefore, it seems appropriate that future conclusions about the presence or absence of cell types should not be drawn without the interrogation of a comprehensive range of cell surface markers.

Considering tubal epithelial cells are known to respond to changes in serum oestrogen and progesterone (Donnez et al., 1985), several studies investigated whether similar changes might occur in the immune cell population of the FT (Ardighieri et al., 2014; Boehme and Donat, 1992; Crow et al., 1994; El-Din Safwat et al., 2008; Geppert et al., 1977; Givan et al., 1997; Hagiwara et al., 1998; Kutteh et al., 1990; Shaw et al., 2011; Suenaga et al., 1998; Ulziibat et al., 2006). Therefore, the effect of menopausal status and cycle phase on tubal immune cell flora were evaluated here. Six studies compared the leucocyte population of pre- and postmenopausal women; however, contradictory findings were reported between authors (Ardighieri et al., 2014; Crow et al., 1994; El-Din Safwat et al., 2008; Geppert et al., 1977; Hagiwara et al., 1998; Mselle et al., 2007). Similarly, identification of lymphocyte fluctuations during the menstrual cycle proved inconsistent between studies (Boehme and Donat, 1992; Crow et al., 1994; Geppert et al., 1977; Givan et al., 1997; Kutteh et al., 1990; Ulziibat et al., 2006). However, it should be noted that the studies by Ardighieri et al. (2014) and Hagiwara et al. (1998) did not report the precise menstrual phase or use of hormonal contraceptives in premenopausal participants, which may profoundly impact the conclusions drawn. The number of macrophages demonstrated a consistent and significant increase during the progesterone-dominant secretory phase compared to the proliferative phase (El-Din Safwat et al., 2008; Shaw et al., 2011; Suenaga et al., 1998). El-Din Safwat et al. (2008) subsequently suggested that steroid hormones might regulate macrophages, highlighting their potential role in tubal functions and even embryonic development. Our review has determined a relationship between reproductive hormones and macrophages in the FT; however, further research into whether this applies to other immune cell types is required.

Of the papers that investigated FT pathology, the majority focused on tubal ectopic pregnancy. In tubal pregnancies, lymphocytes presented a similar distribution to that in non-pregnant healthy tubes (Ardighieri et al., 2014; Boehme and Donat, 1992; Gaytán et al., 2007; Givan et al., 1997; Hagiwara et al., 1998; Rabi et al., 2014a; Ramraj et al., 2018; Suenaga et al., 1998) (Fig. 3). Studies by Geppert et al. (1977) and Ulziibat et al. (2006) presented opposing results regarding the number of lymphocytes in tubal ectopic pregnancy compared to healthy FTs. Given that both these studies were judged as 'poor' based on the risk of bias assessment (Table 2), neither result can be relied upon (Geppert
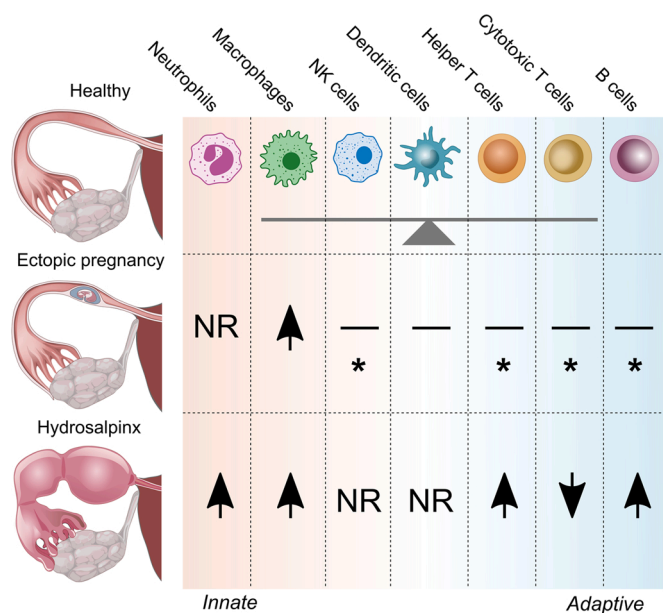
Fig. 3. Overview of immune cell changes in common tubal pathologies. Immune cells of both the innate and adaptive subsystems that have been characterises as major components of the tubal immune flora in health and/or disease are included. Arrows indicate increased or decreased prevalence and dashes indicate no change relative to healthy tubes. Asterisks signify insufficiencies in study quality and/or contradictory findings and/or deficient evidence underpinning the findings. Immune cells not specifically investigated in the current literature are labelled NR (not reported).

et al., 1977; Ulziibat et al., 2006). Other than this instance, the risk of bias assessment could not account for any other inconsistent results presented between studies. In intra-uterine early pregnancy decidua, $CD56^+$ NK cells constitute $> 75\%$ of leucocytes, whilst $CD3^+$ T cells are much lower in abundance (Bulmer et al., 1991). Thus, the T cell dominant, NK cell sparse lymphocyte profile of tubal ectopic pregnancy contrasts with that of intra-uterine early pregnancy decidua (Laskarin et al., 2010; Marx et al., 1999; Pröll et al., 2000; Vassiliadou and Bulmer, 1998; Von Rango et al., 2001; Wicherek et al., 2006; Wicherek et al., 2008).

The macrophage population during tubal implantation was reported to be significantly elevated relative to normal FT (Shaw et al., 2011; Wang et al., 2020) (Fig. 3). Uterine macrophage numbers also increase following pregnancy establishment and account for approximately 20% of leucocytes in intra-uterine decidual tissue (Bulmer et al., 1991, 2010). Wang et al. (2020) hypothesised that these tubal macrophages, regulated by a peptide hormone named adrenomedullin, leave the tubal epithelium more susceptible to embryo implantation via the release of pro-inflammatory and pro-implantation cytokines. This indicates that the number of macrophages present in the tubal epithelium increases before embryo implantation, though the cause for this was not explored. It will be important to focus future studies on how the aberrant tubal immune response encourages ectopic implantation in order to develop preventative strategies for this potentially lethal early pregnancy complication.

Other pathologies of interest identified in this systematic review included salpingitis, hydrosalpinx, pyosalpinx and endometriosis. From the available literature, there is evidence to suggest that cases of salpingitis and hydrosalpinx are associated with evidence of increased innate and adaptive immunological activity (Copperman et al., 2006; Edelstam and Karlsson-Parra, 1996; Haney et al., 1983; Kinnunen et al., 2000; Kutteh et al., 1990; Matsushima et al., 2002; Wang et al., 2020) (Fig. 3). However, this was not seen in cases of pyosalpinx (Geppert et al., 1977). It is important to note that the methodology employed by some studies (flusing the tubal lumen and harvesting cells for flow

cytometric analysis) (Matsushima et al., 2002) may not provide a true representation of the intra-mucosal immune cell population, therefore, the available evidence should be treated with caution. Though only two studies considered the immune cell population in patients with endometriosis, they both identified an increase in the number of tubal macrophages compared to healthy FT (Haney et al., 1983; Matsushima et al., 2002). Collectively, both studies concluded that these macrophages, capable of phagocytosing sperm, may play a causative role in endometriosis-associated infertility (Haney et al., 1983; Matsushima et al., 2002). Due to the lack of studies addressing these heterogenous disorders, more research is required to conclusively define their immune cell profiles and shed light on their contribution to disease aetiology and pathophysiology.

Finally, our review presented five case reports describing lipofuscin-laden histiocyte infiltration in the plicae of tubal mucosa (Gray and Libbey, 2001; Idrees et al., 2007; Suárez-Vilela et al., 2011; Zhang et al., 2012; Zorzi et al., 2010). Though rare, these findings were homogenous between authors and thought to be caused by their close association to endometriosis and PID (Gray and Libbey, 2001; Idrees et al., 2007; Suárez-Vilela et al., 2011; Zhang et al., 2012; Zorzi et al., 2010). Whilst their inflammatory nature is still disputed, terminology such as "xanthogranulomatous salpingitis" (Gray and Libbey, 2001; Idrees et al., 2007; Zhang et al., 2012), "melanosis tubae" (Zorzi et al., 2010), and "pseudoxanthomatous salpingitis" (Suárez-Vilela et al., 2011) have been proposed to describe the pathology most appropriately.

5. Conclusion

The human FT have a distinct population of immune cells representing both the innate and adaptive subsystems. Variations in this population have been observed in several tubal pathologies and are dependent on exposure to reproductive hormones both during the menstrual cycle and after the ovaries cease to produce hormones in the postmenopausal period. However, given the inconsistent evidence presented between studies and the lack of research into tubal pathologies, only limited conclusions can be formulated about this population (Fig. 3). Therefore, future research scope should encompass comprehensive immunophenotyping of the FT in health, including the effect of reproductive hormones on the abundance and function of immune cells. In addition, further investigation into the immune cell populations of pathological tubes would provide a greater understanding of the mechanisms of pathogenesis, potentially leading to the development of treatment innovations in the future. Such studies would greatly benefit from a set of minimal reporting standards and core outcome criteria derived via a consultation process among all expert stakeholders including clinicians, researchers and pathologists (Prins et al., 2018).

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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