



**HAL**  
open science

## **Pregnancy, indoleamine 2,3-dioxygenase (IDO) and chlamydial abortion: An unresolved paradox**

Gary Entrican, Sean Wattedegera, Mara Rocchi, Nicholas Wheelhouse

### ► **To cite this version:**

Gary Entrican, Sean Wattedegera, Mara Rocchi, Nicholas Wheelhouse. Pregnancy, indoleamine 2,3-dioxygenase (IDO) and chlamydial abortion: An unresolved paradox. *Veterinary Microbiology*, 2009, 135 (1-2), pp.98. 10.1016/j.vetmic.2008.09.028 . hal-00532485

**HAL Id: hal-00532485**

**<https://hal.science/hal-00532485>**

Submitted on 4 Nov 2010

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Accepted Manuscript

Title: Pregnancy, indoleamine 2,3-dioxygenase (IDO) and chlamydial abortion: An unresolved paradox

Authors: Gary Entrican, Sean Wattededera, Mara Rocchi, Nicholas Wheelhouse



PII: S0378-1135(08)00395-7  
DOI: doi:10.1016/j.vetmic.2008.09.028  
Reference: VETMIC 4180

To appear in: *VETMIC*

Please cite this article as: Entrican, G., Wattededera, S., Rocchi, M., Wheelhouse, N., Pregnancy, indoleamine 2,3-dioxygenase (IDO) and chlamydial abortion: an unresolved paradox, *Veterinary Microbiology* (2008), doi:10.1016/j.vetmic.2008.09.028

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1

2

3

4 Pregnancy, indoleamine 2,3-dioxygenase (IDO) and chlamydial abortion: an unresolved  
5 paradox

6

7

8 Gary Entrican\*, Sean Wattedegera, Mara Rocchi & Nicholas Wheelhouse

9

10 Moredun Research Institute, Pentlands Science Park, Bush Loan, Midlothian, EH26 0PZ,  
11 United Kingdom

12

13

14

15 Key words: *Chlamydomphila abortus*, pregnancy, infectious abortion, indoleamine 2,3-  
16 dioxygenase, trophoblast

17

18 \*Corresponding author

19 Tel.: +44(0)131 445 511

20 Fax: +44(0)131 445 6235

21 E-mail: [gary.entrican@moredun.ac.uk](mailto:gary.entrican@moredun.ac.uk)

22

23

23

24 **Abstract**

25 *Chlamydomphila abortus* infects the placental trophoblast in sheep, humans and mice,  
26 causing cell damage and inflammation that culminates in abortion. Host control of *C.*  
27 *abortus* appears to be heavily dependant on interferon (IFN)- $\gamma$  production. IFN- $\gamma$  induces  
28 expression of the enzyme indoleamine 2,3-dioxygenase (IDO), resulting in the  
29 degradation of intracellular pools of tryptophan, thereby depriving the organism of this  
30 essential growth nutrient. The anti-chlamydial effects of IFN- $\gamma$  can be reversed by the  
31 addition of exogenous tryptophan. This finding is consistent with studies of the *C.*  
32 *abortus* genome sequence that have revealed that the organism lacks the capability to  
33 synthesise tryptophan from host cell substrates and is therefore dependant on host  
34 tryptophan. This raises an interesting paradox since the placental trophoblast in humans  
35 and mice is known to constitutively express IDO and degrade tryptophan, a phenomenon  
36 that has been linked to maternal immunological tolerance of the semi-allogeneic fetus.  
37 This paradox is discussed in the context of immune modulation during pregnancy,  
38 tryptophan biosynthesis by *Chlamydiaceae* and differences in placental structures  
39 between sheep, humans and mice.

40

## 40 Introduction

41 The nine species of obligate intracellular Gram-negative bacteria that belong to the  
42 genera *Chlamydia/Chlamydophila* can infect a variety of hosts and cause a wide range of  
43 diseases (Longbottom and Coulter, 2003). Different species of  
44 *Chlamydia/Chlamydophila* preferentially infect different anatomical sites within their  
45 hosts, with epithelial cells at mucosal surfaces being the primary target for infection. In  
46 some cases, infection and disease may be restricted to mucosal epithelium (e.g. the  
47 trachoma biovar of *C. trachomatis*) or the infection may disseminate to cause disease at  
48 other sites (e.g. *C. pneumoniae*, *C. abortus*). The factors that determine tissue tropism  
49 and host tropism of different *Chlamydia/Chlamydophila* species are not entirely clear, but  
50 evidence from genome sequences indicates that the ability to acquire or synthesise  
51 nutrients in the face of intracellular host immune defence mechanisms induced by  
52 interferon (IFN)- $\gamma$  plays an important role, particularly during persistent infections  
53 (Nelson et al., 2005).

54

55 Among all the species of *Chlamydia/Chlamydophila*, *C. abortus* has a particular affinity  
56 for the placenta, causing abortion in ruminants, humans and mice (Longbottom and  
57 Coulter, 2003). On one hand, the placenta could be considered as a favourable site for *C.*  
58 *abortus* since expression of inflammatory cytokines such as IFN- $\gamma$  tend to be highly  
59 restricted at the maternofetal interface (Entrican, 2002a). On the other hand, the placenta  
60 could be regarded as an unfavourable site for *C. abortus* since trophoblast cells in  
61 humans and mice constitutively express indoleamine 2,3-dioxygenase (IDO) (Sedlmayr,  
62 2007). IDO is an IFN- $\gamma$ -inducible enzyme that degrades tryptophan, an essential amino

63 acid for *C. abortus* growth (Entrican, 2002a; Entrican, 2004; Thomson et al., 2005). It is  
64 therefore paradoxical that an organism such as *C. abortus* that is auxotrophic for  
65 tryptophan should infect trophoblast. To address this paradox we need to elucidate the  
66 intracellular host defence pathways that control *C. abortus* growth, identify the  
67 biosynthetic pathways encoded by the pathogen that dictate its ability to survive under  
68 restricted nutrient conditions, and define the specialised nature of trophoblast that permit  
69 survival of the semi-allogeneic fetus in the face of adaptive maternal immunity.

70

#### 71 **IFN- $\gamma$ , IDO, tryptophan and control of chlamydial growth**

72 The link between IFN- $\gamma$ -induced tryptophan degradation, IDO and control of chlamydial  
73 growth was first described in detail in human uroepithelial cells infected with the 6BC  
74 strain of *C. psittaci*. The production of N-formylkynurenine in the IFN- $\gamma$ -treated cells was  
75 indicative of tryptophan catabolism by IDO (Byrne et al., 1986). This anti-chlamydial  
76 host defence pathway has since been reported to operate in many different cell types  
77 infected with *Chlamydiaceae* species, although it is not ubiquitous across host species.  
78 For example, IFN- $\gamma$ -inducible IDO appears to be a predominant anti-chlamydial  
79 intracellular defence pathway in human cells, whereas IFN- $\gamma$ -inducible nitric oxide  
80 synthase (iNOS) appears to be the predominant defence pathway in mouse cells (Roshick  
81 et al., 2006). To date, no evidence has been found for iNOS as an anti-chlamydial  
82 defence mechanism in sheep, whereas there is strong evidence for IDO and tryptophan  
83 degradation. The addition of exogenous tryptophan to ovine cells *in vitro* reverses IFN- $\gamma$ -  
84 mediated restriction of *C. abortus* growth (Brown et al., 2001) and IFN- $\gamma$  induces the

85 expression of IDO in ovine cells (Figure 1). These observations suggest that *C. abortus* is  
86 not capable of synthesising its own tryptophan.

87

### 88 **Tryptophan biosynthesis by *Chlamydiaceae***

89 There are five genes in the tryptophan operon that are necessary for the biosynthesis of  
90 tryptophan from chorismate as a substrate. These are designated *trpA*, *trpB*, *TrpC*, *TrpD*  
91 and *trpE*, with *trpA* and *trpE* each having an  $\alpha$  and  $\beta$  subunit (Xie et al., 2002). The  
92 identification of tryptophan deprivation as an intracellular defence mechanism to restrict  
93 chlamydial growth preceded the sequencing and annotation of the *Chlamydiaceae*  
94 genomes that are now available. To date, no complete tryptophan operon has been  
95 described in any genome sequence of *Chlamydiaceae*, which explains the effectiveness of  
96 IFN- $\gamma$ -induced tryptophan catabolism in restricting chlamydial multiplication. However,  
97 *Chlamydiaceae* species do differ in their complement of genes encoding components of  
98 the tryptophan operon within their plasticity zones (PZ), which appears to be linked to  
99 their pathogenesis. The genome of *C. pneumoniae* lacks all genes of the tryptophan  
100 operon whereas the genome of *C. psittaci* has an almost complete tryptophan operon,  
101 lacking only the *trpA $\alpha$*  and *trpA $\beta$*  genes (Xie et al., 2002). This provides an opportunity  
102 for *C. psittaci* to synthesise tryptophan from kynurenine and thereby to potentially  
103 survive and persist in the presence of high levels of IDO expression (assuming that host  
104 ATP and host serine are also available). This biosynthetic survival strategy is clearly not  
105 an option for *C. pneumoniae* that relies on host cell tryptophan. Tryptophan availability  
106 has been linked to the tissue tropism of the trachoma biovar of *C. trachomatis*. Genital  
107 serovars of *C. trachomatis* encode functional tryptophan synthase genes that permit the

108 synthesis of tryptophan from indole produced by genital microflora (Caldwell et al.,  
109 2003). Ocular serovars of *C. trachomatis* have mutated tryptophan synthase genes and  
110 exhibit an absolute requirement for tryptophan. This theoretically makes ocular serovars  
111 more susceptible to IFN- $\gamma$ -mediated IDO expression than genital serovars (McClarty et  
112 al., 2007).

113

114 Thus, although the factors that govern tissue tropism of *Chlamydiaceae* are not fully  
115 elucidated, the biosynthetic pathways that allow organisms to survive in the presence of  
116 IFN- $\gamma$ -induced intracellular host defence pathways appear to be important. Pathogen  
117 genome sequences are an invaluable resource in defining such factors. Additionally,  
118 improvements in molecular typing of *Chlamydiaceae* will provide a clearer picture of  
119 pathogen load, identify strains and/or species associated with disease pathogenesis. Such  
120 information will ultimately inform on control strategies and may even challenge current  
121 paradigms of chlamydial infections and why certain organisms preferentially infect  
122 certain sites or certain hosts. This is already becoming apparent with the identification of  
123 previously-unrecognised *C. psittaci* and *C. pneumoniae* infections in the conjunctiva of  
124 patients with trachoma (Dean et al., 2008). The link between such infections and IFN- $\gamma$ -  
125 induced host defence pathways will be interesting, particularly since this is likely to  
126 extend beyond tissue-tropism into host-tropism of *Chlamydiaceae*. For example, *C.*  
127 *muridarum* appears to have evolved mechanisms to survive the effects of IFN- $\gamma$  in murine  
128 epithelial cells by circumventing the inducible GTPases, rather than IDO (Nelson et al.,  
129 2005).

130



131 Like *C. pneumoniae*, the PZ of the genome of the S26/3 isolate of *C. abortus* lacks the  
132 tryptophan operon gene cluster. Moreover, the PZs in six other *C. abortus* strains from  
133 sheep, cattle and goats (including the vaccine strains A22 and 1B) do not vary  
134 significantly from the S26/3 strain (Thomson et al., 2005). Thus, dependency on host  
135 tryptophan is a common feature of *C. abortus* isolates. The question is: how does this  
136 equate with tropism for placental trophoblast? To attempt to answer that question we  
137 need to look at the function of the trophoblast at the maternofetal interface.

138

### 139 **IDO and pregnancy**

140 One of the basic principles of modern immunology is the Clonal Selection Model. This  
141 states that immunological tolerance is acquired, that the immune system can discriminate  
142 between self and nonself and respond accordingly to combat infectious agents and reject  
143 foreign tissue grafts (Burnet, 1959). A logical extension of the model is the prediction  
144 that eutherian (placental) mammals should reject the semi-allogeneic fetus. This does not  
145 occur and therefore presents a challenge to the model. It was recognised by Peter  
146 Medawar that certain conditions would have to be met for mammalian pregnancy to be  
147 accommodated within the self-nonself model of immune activation (Medawar, 1953).  
148 One of these conditions was that the placenta acts as a barrier between mother and fetus,  
149 thereby preventing maternal rejection. However, this is an over-simplified concept, since  
150 placentation and the degree of contact between fetal cells and maternal tissues (and  
151 maternal blood) varies greatly between mammals. Pigs and horses have the least invasive  
152 (epitheliochorial) placentation whereas humans and mice have the most invasive  
153 (hemochorial) placentation (Moffett and Loke, 2006). These structural differences mean

154 that immunological comparisons relating to reproduction in different species must be  
155 drawn with care. Most of our current knowledge has been derived from studies in mice  
156 and humans, and how these relate to sheep that have a synepitheliochorial placenta is  
157 debatable.

158

159 It is beyond the scope of this review to cover all of the mechanisms thought to be  
160 involved in maternal tolerance of the semi-allogeneic fetus that are reviewed elsewhere  
161 (Rocchi et al, submitted), but one is of particular interest: trophoblast expression of IDO.  
162 Given that *C. abortus* is a natural pathogen of humans and ruminants, and that mouse  
163 models of chlamydial abortion have been developed, there are comparisons to be drawn  
164 across these species.

165

166 The role of IDO in the maintenance of pregnancy came to prominence when it was found  
167 that pregnant mice treated with a metabolic inhibitor of IDO experienced pregnancy  
168 failure (abortion/resorption). Abortion only occurred when female mice were mated with  
169 males of a different major histocompatibility complex (MHC) haplotype and carrying  
170 semi-allogeneic fetuses and not when mated with males of the same MHC haplotype and  
171 therefore carrying syngeneic fetuses (Munn et al., 1998). The mechanism of abortion was  
172 found to be breakdown of tolerance of maternal CD8+ve T cells to paternal MHC class I  
173 molecules expressed by the fetus, elucidated by adoptive transfer of transgenic CD8+ve T  
174 cells in the pregnant, treated mice. The interpretation of these experiments has been  
175 challenged with the argument that by degrading tryptophan to kynurenine, IDO prevents  
176 tryptophan catabolism to serotonin. Serotonin is a potent vasoconstrictor and would be

177 undesirable in the placenta since it could restrict blood flow to the fetus, resulting in  
178 tissue damage and abortion (Bonney and Matzinger, 1998). Reduced IDO expression in  
179 human placenta has been linked to pre-eclampsia, a disorder of restricted placental blood  
180 flow (Kudo et al., 2003; Nishizawa et al., 2007). IDO may therefore have both a  
181 physiological and immunological role in mammalian reproduction (Entrican, 2004).

182

183 In the highly-invasive haemochorial placentation of humans and mice, trophoblast cells  
184 of the chorionic epithelium infiltrate maternal blood vessels and come into direct contact  
185 with maternal blood. In the mouse it is the outer layer (and thus most invasive)  
186 trophoblast giant cells of the placenta that express IDO (Baban et al., 2004). The  
187 analogous cells in humans are the extravillous cytotrophoblasts that express IDO in the  
188 first trimester of pregnancy (Honig et al., 2004). However unlike the mouse, the  
189 expression of IDO is not completely restricted to the extravillous cytotrophoblast. Several  
190 studies have demonstrated the presence of IDO expression in the villous  
191 syncytiotrophoblast in first trimester and term placenta (Sedlmayr et al., 2002; Kudo et al.,  
192 2004; Ligam et al., 2005). The expression of IDO in trophoblast of other placental types  
193 has not been studied in any detail and not to our knowledge in sheep or goats. Sheep have  
194 a cotyledonary, synepitheliochorial placenta in which there are discreet attachment points  
195 between the chorioallantois and the endometrium (the placentome) (Wooding and Flint,  
196 1999). Within the placentome there is fusion between the uterine epithelium and  
197 trophoblast to form structures known as syncytial plaques (Igwebuike, 2006). There is  
198 therefore a limited degree of invasion of cells of fetal origin into maternal tissue (Figure  
199 2), suggesting that some maternal immunological tolerance of the fetus is required.

200

201 **The paradox of placental IDO expression and chlamydial abortion**

202 Since IDO is expressed by human and mouse trophoblast, it is intriguing that both can  
203 experience chlamydial abortion (Wong et al., 1985; Kerr et al., 2005). Why would *C.*  
204 *abortus*, an organism that lacks a tryptophan operon, have tropism for a tissue where  
205 tryptophan is degraded? One possibility is that the cells targeted by *C. abortus* are not the  
206 cells expressing IDO. In aborted human placenta, *C. abortus* antigen is detected within  
207 the villous trophoblast by immunolabelling (Figure 3). To date there has been no attempt  
208 to ascertain whether the infected cells are syncytiotrophoblast or villous cytotrophoblast,  
209 or if infected cells do indeed express IDO. This is theoretically possible since there are  
210 antibodies to human IDO that have been used to stain trophoblast, but with conflicting  
211 results. Studies on human term placenta report strong IDO staining (Kudo et al., 2004),  
212 low grade staining (Nishizawa et al., 2007), patchy staining (Sedlmayr et al., 2002) or no  
213 IDO staining (Ligam et al., 2005). These differences cannot be attributed to the antibody  
214 specificity since all four used the same antibody from the same source. However,  
215 immunolabelling is a highly complex technique that is affected by many parameters,  
216 including tissue processing, antigen retrieval and staining protocols, all of which may  
217 contribute to the different outcomes reported.

218

219 There are few *in vitro* studies of *C. abortus* infection of trophoblast, although the human  
220 BeWo choriocarcinoma trophoblast line has been used as a target. However, BeWo cells  
221 not only fail to constitutively express IDO, it cannot be induced by IFN- $\gamma$ , despite the  
222 expression of IFN- $\gamma$  receptor (Entrican et al., 2002b). The apparent paradox of placental

223 expression of IDO and *C. abortus* infection remains to be resolved. However, there are  
224 several potential experimental approaches to address this. Firstly, primary human  
225 trophoblast constitutively expressing IDO could be experimentally infected *in vitro* with  
226 *C. abortus*; secondly, IDO gene knockout mice could be infected with *C. abortus*; and  
227 thirdly, and most importantly from the point of view of ovine enzootic abortion, probes  
228 could be developed to study IDO expression in sheep placenta. We are in the process of  
229 cloning the full-length ovine IDO cDNA with a view to addressing this question.

230

### 231 **Conclusions**

232 It remains unclear if *C. abortus* overcomes constitutive IDO expression in trophoblast or  
233 if *C. abortus* preferentially targets trophoblast in which IDO is low or absent. The first  
234 scenario may be less likely given the lack of a tryptophan operon in *C. abortus* whereas  
235 the second scenario is a more realistic hypothesis and one that can be addressed  
236 experimentally. Probes are being developed to study IDO expression in the trophoblast. It  
237 will be of interest to examine IDO expression at different stages of gestation in sheep  
238 since its expression could be temporally controlled.

239

240 Finally, it is worth commenting that the role of IFN- $\gamma$  and IDO as a host defence  
241 mechanism against *Chlamydia/Chlamydophila* doesn't always fit the current paradigms.  
242 As mentioned earlier, the ocular serovars of *C. trachomatis* lack any capability of  
243 synthesising tryptophan and therefore appear to be highly susceptible to IDO (Nelson et  
244 al., 2005). However, in a recent study of patients with trachoma, a positive correlation  
245 was found between pathogen load and the expression of *IFN- $\gamma$*  and *IDO* transcripts in

246 conjunctival epithelia (Faal et al., 2006). This is in conflict with the *C. trachomatis*  
247 genome data, although the underlying reasons remain unclear. That particular study was  
248 conducted prior to the discovery that *C. pneumoniae* and *C. psittaci* could infect the  
249 human conjunctiva (Dean et al., 2008). However, given that *C. pneumoniae* lacks a  
250 tryptophan operon, the same IFN- $\gamma$ -mediated principle host defence mechanism would be  
251 expected to apply. The fact that it does not indicates that we have many remaining  
252 unanswered questions regarding chlamydial pathogenesis and host immunity.

253

254

#### 255 **Conflict of interest statement**

256 None of the authors (GE, MR, SW, NW) has a financial or personal relationship with  
257 other people or organisations that could inappropriately influence or bias the paper  
258 entitled “Pregnancy, indoleamine 2,3-dioxygenase (IDO) and chlamydial abortion: an  
259 unresolved paradox”.

260

261

#### 262 **Acknowledgements**

263 This work was funded by the Scottish Government, Rural and Environment Research and  
264 Analysis Directorate (RERAD). The authors thank Dr David Buxton for helpful  
265 discussions and for providing the image of human placenta infected with *C. abortus*.

266

266 Figure legends

267 **Figure 1**

268 Ovine ST-6 fibroblast cells were cultured for 24 hours in the presence of 250U/ml  
269 recombinant ovine interferon (IFN)- $\gamma$ . Cells were lysed, RNA was prepared using a  
270 Qiagen RNeasy™ kit and then reverse transcribed using Taqman® reverse transcription  
271 reagents (Applied Biosystems) according to the manufacturer's instructions. The cDNA  
272 encoding ovine IDO was amplified using primers based on the published human IDO  
273 sequence (forward 5'-CCTGACTTATGAGAACATGGACG-3', reverse 5'-  
274 GAAGTTCCTGTGAGCTGGTG-3'). A 493 bp fragment of expected size was observed  
275 in cells treated with IFN- $\gamma$  (lane 3) that was not present in untreated cells (lane 2). The  
276 molecular weight reference ladder is shown in lane 1.

277

278 **Figure 2**

279 Schematic representation of the migration of ovine binucleate fetal trophoblast cells (1)  
280 as they invade (2) and fuse (3) with maternal uterine cells to form feto-maternal hybrid  
281 syncytial plaques (4). Blood vessels are indicated at either side of the materno-fetal  
282 interface and there is no mixing of maternal and fetal blood.

283

284 **Figure 3**

285 A section of placenta from a human case of abortion caused by *C. abortus* showing  
286 lipopolysaccharide (LPS) of *C. abortus* localising to trophoblast surrounding placental  
287 villi. Immunolabelling was conducted with a primary anti-LPS mouse monoclonal  
288 antibody (13/4) and a second-stage anti-mouse peroxidase conjugate.

289  
290

## References

- 291 Baban,B., Chandler,P., McCool,D., Marshall,B., Munn,D.H. and Mellor,A.L., 2004.  
292 Indoleamine 2,3-dioxygenase expression is restricted to fetal trophoblast giant  
293 cells during murine gestation and is maternal genome specific. J. Reprod.  
294 Immunol. 61, 67-77.
- 295 Bonney,E.A. and Matzinger,P., 1998. Much IDO about pregnancy. Nat. Med. 4, 1128-  
296 1129.
- 297 Brown,J., Howie,S.E.M. and Entrican,G., 2001. A role for tryptophan in control of  
298 chlamydial abortion in sheep. Vet. Immunol. Immunopathol. 82, 107-119.
- 299 Burnet,F.M., 1959. Clonal Selection Theory of Acquired Immunity. Vanderbilt and  
300 Cambridge University Presses.
- 301 Byrne,G.I., Lehmann,L.K. and Landry,G.J., 1986. Induction of tryptophan catabolism is  
302 the mechanism for gamma-interferon-mediated inhibition of intracellular  
303 *Chlamydia psittaci* replication in T24 cells. Infect. Immun. 53, 347-351.
- 304 Caldwell,H.D., Wood,H., Crane,D., Bailey,R., Jones,R.B., Mabey,D., Maclean,I.,  
305 Mohammed,Z., Peeling,R., Roshick,C., Schachter,J., Solomon,A.W.,  
306 Stamm,W.E., Suchland,R.J., Taylor,L., West,S.K., Quinn,T.C., Belland,R.J. and  
307 McClarty,G., 2003. Polymorphisms in *Chlamydia trachomatis* tryptophan  
308 synthase genes differentiate between genital and ocular isolates. J. Clin. Invest.  
309 111, 1757-1769.



- 310 Dean,D., Kandel,R.P., Adhikari,H.K. and Hessel,T., 2008. Multiple *Chlamydiaceae*  
311 species in trachoma: implications for disease pathogenesis and control. PLoS  
312 Med. 5, e14.
- 313 Entrican,G., 2002a. Immune regulation during pregnancy and host-pathogen interactions  
314 in infectious abortion. J. Comp Pathol. 126, 79-94.
- 315 Entrican,G., Wattedgedera,S., Chui,M., Oemar,L., Rocchi,M. and McInnes,C., 2002b.  
316 Gamma interferon fails to induce expression of indoleamine 2,3-dioxygenase  
317 and does not control the growth of *Chlamydomphila abortus* in BeWo trophoblast  
318 cells. Infect. Immun. 70, 2690-2693.
- 319 Entrican,G., 2004. IDO: a crossroads of immunology and physiology? J. Reprod.  
320 Immunol. 61, 63-65.
- 321 Faal,N., Bailey,R.L., Jeffries,D., Joof,H., Sarr,I., Laye,M., Mabey,D.C. and Holland,M.J.,  
322 2006. Conjunctival FOXP3 expression in trachoma: do regulatory T cells have a  
323 role in human ocular *Chlamydia trachomatis* infection? PLoS Med. 3, e266.
- 324 Honig,A., Rieger,L., Kapp,M., Sutterlin,M., Dietl,J. and Kammerer,U., 2004.  
325 Indoleamine 2,3-dioxygenase (IDO) expression in invasive extravillous  
326 trophoblast supports role of the enzyme for materno-fetal tolerance. J. Reprod.  
327 Immunol. 61, 79-86.
- 328 Igwebuike,U.M., 2006. Trophoblast cells of ruminant placentas--A minireview. Anim  
329 Reprod. Sci. 93, 185-198.

- 330 Kerr,K., Entrican,G., McKeever,D. and Longbottom,D., 2005. Immunopathology of  
331 *Chlamydophila abortus* infection in sheep and mice. Res. Vet. Sci. 78, 1-7.
- 332 Kudo,Y., Boyd,C.A., Sargent,I.L. and Redman,C.W., 2003. Decreased tryptophan  
333 catabolism by placental indoleamine 2,3-dioxygenase in preeclampsia. Am. J.  
334 Obstet. Gynecol. 188, 719-726.
- 335 Kudo,Y., Boyd,C.A., Spyropoulou,I., Redman,C.W., Takikawa,O., Katsuki,T., Hara,T.,  
336 Ohama,K. and Sargent,I.L., 2004. Indoleamine 2,3-dioxygenase: distribution and  
337 function in the developing human placenta. J. Reprod. Immunol. 61, 87-98.
- 338 Ligam,P., Manuelpillai,U., Wallace,E.M. and Walker,D., 2005. Localisation of  
339 indoleamine 2,3-dioxygenase and kynurenine hydroxylase in the human placenta  
340 and decidua: implications for role of the kynurenine pathway in pregnancy.  
341 Placenta 26, 498-504.
- 342 Longbottom,D. and Coulter,L.J., 2003. Animal chlamydioses and zoonotic implications.  
343 J. Comp Pathol. 128, 217-244.
- 344 McClarty,G., Caldwell,H.D. and Nelson,D.E., 2007. Chlamydial interferon gamma  
345 immune evasion influences infection tropism. Curr. Opin. Microbiol. 10, 47-51.
- 346 Medawar,P.B., 1953. Some immunological and endocrinological problems raised by the  
347 evolution of viviparity in vertebrates. Symposia of the Society of Experimental  
348 Biology 7, 320-338.

- 349 Moffett,A. and Loke,C., 2006. Immunology of placentation in eutherian mammals. Nat.  
350 Rev. Immunol. 6, 584-594.
- 351 Munn,D.H., Zhou,M., Attwood,J.T., Bondarev,I., Conway,S.J., Marshall,B., Brown,C.  
352 and Mellor,A.L., 1998. Prevention of allogeneic fetal rejection by tryptophan  
353 catabolism. Science 281, 1191-1193.
- 354 Nelson,D.E., Virok,D.P., Wood,H., Roshick,C., Johnson,R.M., Whitmire,W.M.,  
355 Crane,D.D., Steele-Mortimer,O., Kari,L., McClarty,G. and Caldwell,H.D., 2005.  
356 Chlamydial IFN-gamma immune evasion is linked to host infection tropism.  
357 Proc. Natl. Acad. Sci. U. S. A. 102, 10658-10663.
- 358 Nishizawa,H., Hasegawa,K., Suzuki,M., Kamoshida,S., Kato,T., Saito,K., Tsutsumi,Y.,  
359 Kurahashi,H. and Udagawa,Y., 2007. The etiological role of allogeneic fetal  
360 rejection in pre-eclampsia. Am. J. Reprod. Immunol. 58, 11-20.
- 361 Roshick,C., Wood,H., Caldwell,H.D. and McClarty,G., 2006. Comparison of gamma  
362 interferon-mediated antichlamydial defense mechanisms in human and mouse  
363 cells. Infect. Immun. 74, 225-238.
- 364 Sedlmayr,P., Blaschitz,A., Wintersteiger,R., Semlitsch,M., Hammer,A., MacKenzie,C.R.,  
365 Walcher,W., Reich,O., Takikawa,O. and Dohr,G., 2002. Localization of  
366 indoleamine 2,3-dioxygenase in human female reproductive organs and the  
367 placenta. Mol. Hum. Reprod. 8, 385-391.
- 368 Sedlmayr,P., 2007. Indoleamine 2,3-dioxygenase in materno-fetal interaction. Curr. Drug  
369 Metab. 8, 205-208.

370 Thomson,N.R., Yeats,C., Bell,K., Holden,M.T., Bentley,S.D., Livingstone,M., Cerdeno-  
371 Tarraga,A.M., Harris,B., Doggett,J., Ormond,D., Mungall,K., Clarke,K.,  
372 Feltwell,T., Hance,Z., Sanders,M., Quail,M.A., Price,C., Barrell,B.G., Parkhill,J.  
373 and Longbottom,D., 2005. The *Chlamydophila abortus* genome sequence reveals  
374 an array of variable proteins that contribute to interspecies variation. *Genome*  
375 *Res.* 15, 629-640.

376 Wong,S.Y., Gray,E.S., Buxton,D., Finlayson,J. and Johnson,F.W., 1985. Acute  
377 placentitis and spontaneous abortion caused by *Chlamydia psittaci* of sheep  
378 origin: a histological and ultrastructural study. *J. Clin. Pathol.* 38, 707-711.

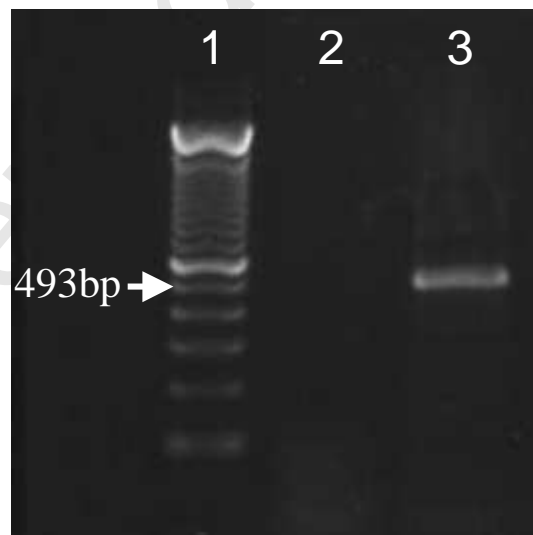
379 Wooding,F.B.P. and Flint,A.P.F., 1999. Placentation. In: G.E.Lamming (Ed.) *Pregnancy*  
380 *and Lactation.* [Chapman & Hall], pp. 235-429.

381 Xie,G., Bonner,C.A. and Jensen,R.A., 2002. Dynamic diversity of the tryptophan  
382 pathway in chlamydiae: reductive evolution and a novel operon for tryptophan  
383 recapture. *Genome Biol.* 3, research0051.

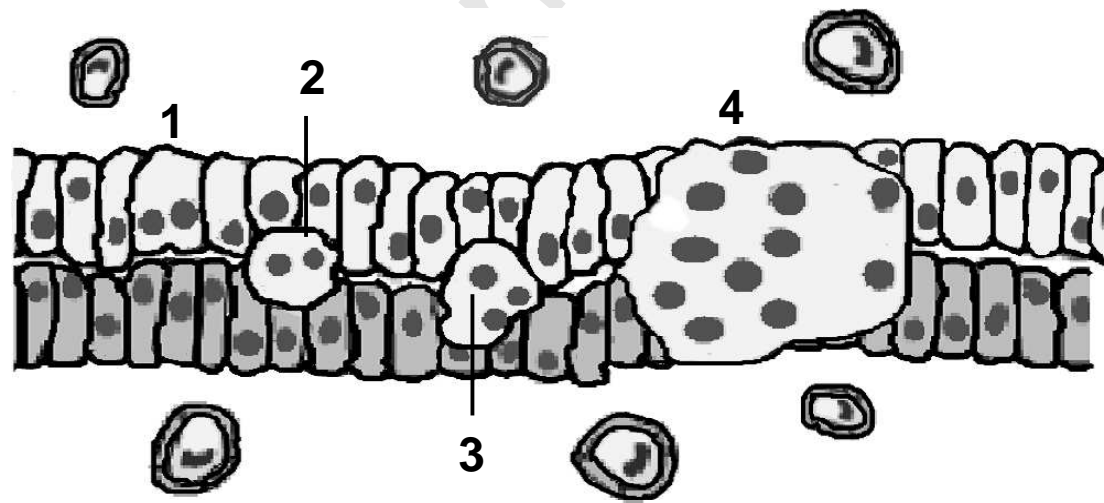
384

385

386



Fetal



Maternal

