

1 A Reappraisal: The Natural History of Amniote Reproductive Modes In Light of Comparative  
2 Evolutionary Genomics

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10 **Abstract**

11

12 There is a current lack of consensus on the ancestral parity mode, oviparity (egg-laying) and  
13 viviparity (live-birth), of amniotes and squamates (snakes and lizards). How transitions between  
14 parity modes occur at the genomic level has primary importance on how science conceptualizes  
15 the origin of amniotes, and highly variable parity modes in Squamata. Within the context of  
16 interdisciplinary literature—medical, poultry science, reproductive biology, and evolutionary  
17 biology—I review the genomics and physiology of five broad processes (Main Five) expected to  
18 change during transitions between parity modes: eggshell formation, embryonic retention,  
19 placentation, calcium transport, and maternal-fetal immune dynamics. Throughout, I offer  
20 alternative perspectives and testable hypotheses regarding proximate causes of parity mode  
21 evolution in amniotes and squamates. Should viviparity have evolved early in the history of  
22 Lepidosauria, I offer the basal cap hypothesis as a proximate explanation. The framework of this  
23 hypothesis can be extended to amniotes to infer their ancestral state. Medawar’s paradigm  
24 contextualizes embryos as analogous to allografts. However, an abundance of research across  
25 mammals, birds, and reptiles demonstrates that the maternal immune response to  
26 gestation/gravidity cannot be explained by immunosuppression, inertness, evasion, or  
27 immunological barriers. However, a rare example of a species with an apparently inert response  
28 to oviparous gravidity is *Lampropholis guichenoti*, an oviparous skink that differentially  
29 expresses zero genes during gravidity—making it a reasonable model for the original amniote  
30 egg. Overall, this review grounds itself in the historical literature while offering a modern  
31 perspective on a subject that has fascinated scientists for centuries—the origin of amniotes.  
32 Based on the cumulative evidence across the Main Five, I provide a mechanism through which

33 squamates may reverse back to oviparity; and make predictions on the directionality of  
34 transitions in three reproductively bimodal species. I encourage the scientific community to  
35 utilize this manuscript as a resource in comparative genomics studies, embrace the complexity of  
36 the system, and thoughtfully consider the framework proposed.

37 *Key Words:* reproductive mode, parity modes, oviparity, squamates, eggshell deposition,  
38 embryonic retention, embryonic calcium transport, maternal-fetal interface, comparative  
39 evolutionary physiology.

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41	<b>Contents</b>	
42	I. Introduction.....	7
43	(1) Terminology.....	14
44	(2) Main five physiological changes of parity mode transitions.....	14
45	II. Length of Embryonic Retention.....	15
46	(1) Parturition & oviposition.....	15
47	(i) Quiescence & sustained progesterone production in	
48	reproductive tissues.....	16
49	(ii) Activation & progesterone withdrawal.....	20
50	(iii) Stimulation & electrical gradients, inflammation, and	
51	hormonal regulation.....	21
52	(2) Unique qualities of oviposition & parturition in	
53	Sauropsids.....	27
54	(3) Pre-term birth & embryonic retention mechanisms.....	28
55	(4) Discussion & future directions—embryonic retention and	
56	parity mode evolution.....	29
57	III. Eggshell Formation.....	30
58	(1) Mineral composition of eggshells.....	32
59	(2) Uterine glands & the evolution of parity modes.....	34
60	(3) Evolutionary implications of the physiology of eggshell formation.....	36
61	(4) Pleiotropy of genes and proteins involved with eggshell formation.....	43
62	(5) Eggshell formation termination.....	46
63	(6) Rotating the egg for eggshell formation.....	47

64	(7) Discussion & future directions—eggshell formation &	
65	parity mode evolution.....	48
66	IV. Placentation & Transport of Embryonic Water, Gas, and Nutrients.....	49
67	(1) Anatomy & methods of water, gas & nutrient provisioning.....	49
68	(2) Evolutionary history of yolk-sac formation and yolk processing.....	51
69	(3) Evolutionary history of placentrophy in mammals & squamates.....	52
70	(4) Genes involved with embryonic water, gas, and nutrient transport.....	55
71	(5) Uterine glands: adenogenesis, placenta development and histotrophy.....	61
72	(6) Discussion & future directions—embryonic nutrients, gas	
73	and water supply.....	64
74	V. Embryonic Calcium Provisioning.....	66
75	(1) Phylogenetic context of embryonic calcium sources.....	66
76	(2) Hypotheses on calcium mobilization and the evolution of parity modes.....	67
77	(3) Embryonic calcium provisioning mechanisms.....	71
78	(4) Discussion & future directions—calcium provisioning and parity	
79	mode evolution.....	74
80	VI. Maternal-Fetal Immune Dynamics.....	75
81	(1) Comparing amniote immune systems.....	76
82	(2) Medawar’s paradigm.....	77
83	(3) Perspectives on the evolution of the uterine immune system.....	78
84	(4) Implications of the reptilian immune system and morphology on	
85	parity mode evolution.....	80
86	(5) The inflammation paradox.....	82

87	(6) Inertness and barriers at the maternal-fetal interface.....	83
88	(7) T cell populations and mammalian viviparity.....	84
89	(8) Progesterone, cytokines, and maternal-fetal immune dynamics.....	85
90	(9) The major histocompatibility complex and maternal-fetal	
91	immune dynamics.....	87
92	(10) Microchimerism and maternal-fetal immune dynamics.....	90
93	(11) Paternal alloantigens.....	91
94	(12) Discussion and future directions—maternal-fetal immune dynamics	
95	& parity mode evolution.....	93
96	VII. Conclusions.....	95
97	VIII. Acknowledgements.....	99

98 **I. Introduction**

99

100 A reappraisal is needed for the conceptual framework used to research the evolution of  
101 oviparity (egg-laying) and viviparity (live-birth) in amniotes (birds, non-avian reptiles, and  
102 mammals). Squamates (snakes and lizards) are unique amongst amniotes because they have  
103 highly variable parity modes (Figure 1). Beginning with the first phylogenetic analyses on the  
104 subject, a warm-blooded scientific disagreement has persisted over the labile nature of  
105 evolutionary transitions between parity modes (Blackburn, 1999, 2015; de Fraipont, Clobert &  
106 Barbault, 1996; Griffith et al., 2015; Harrington & Reeder, 2017; Lee & Shine, 1998; Pyron,  
107 2015; Pyron & Burbrink, 2014; Recknagel et al., 2018, 2021b). A growing number of  
108 transcriptomic and genomic studies analyzing the molecular underpinnings of reproductive mode  
109 evolution in squamates (e. g., Brandley et al. 2012; Cornetti et al. 2018; Gao et al. 2019; Griffith et al.  
110 2016, 2017; Foster et al. 2020, 2022; Recknagel et al. 2021a; Yurchenko et al. 2020; Xie et al. 2022) and  
111 recent advances on the ancestral state of amniotes and dinosaurs contribute to this discussion (Jiang et  
112 al., 2023; Norell et al., 2020). It is prudent to acknowledge that the relative difficulty of changing  
113 phenotypes cannot be determined from morphology alone or unidentified physiological  
114 mechanisms. At least theoretically, any phenotypic change could be facilitated by simple  
115 genomic changes (e.g., a single nucleotide polymorphism) or any combination of multi-omic  
116 changes to any number of loci. As research begins to reveal the molecular networks involved  
117 with parity mode evolution, it is important to avoid bias that could be introduced by assumptions  
118 on the feasibility of transitions. Through synthesis of modern and historical research on amniote  
119 reproduction, this review aims to provide greater context for hypotheses testing on ancestral  
120 states of parity modes in amniotes and squamates.

121           The earliest estimates predicted that viviparity evolved independently between 90-100  
122 times in squamates (Blackburn, 1982, 1985, 1992). These estimates assumed that oviparity was  
123 the ancestral state and, based on the theoretical grounds of Dollo's law, that reversals back to  
124 oviparity should be exceedingly rare (Blackburn, 1992; Fitch, 1970; Neill, 1964; Tinkle &  
125 Gibbons, 1977). An intermediate phenotype of re-evolving an eggshell has been considered as  
126 physiologically unviable, preventing reversals (Blackburn, 1995; Griffith et al., 2015). This was  
127 demonstrated when experimentally induced extended egg retention in phrynosomatid lizards  
128 resulted in adverse embryonic development attributed to impeded gas exchange imposed by the  
129 eggshell (Mathies & Andrews, 1999, 2000; Parker & Andrews, 2006). However, this result may  
130 be clade-specific.

131           Intermediate phenotypes as fitness valleys assumes 1) eggshells inherently impede gas-  
132 exchange and 2) that an eggshell must re-evolve before a reversal back to oviparity is possible  
133 (Griffith et al., 2015). Contrarily, eggshells are considered a component of the placenta in  
134 viviparous Rough Earth Snakes, *Haldea striatula*, and in viviparous reproductively bimodal  
135 European Common Lizards, *Zootoca vivipara* and Yellow-bellied Three-toed Skinks, *Saiphos*  
136 *equalis* (Stewart, 2013). Additionally, *Saiphos equalis* is a reproductively bimodal skink that has  
137 an oviparous population with incubation times as short as 5 days, thus embryos spend significant  
138 time in utero with an eggshell (Smith et al., 2001). Another surprising example of eggshells  
139 being compatible with full embryonic development includes a report of a captive tortoise that  
140 retained viable eggs until the hatching stage (Kuchling & Hofmeyr, 2022).

141           Several studies predict early origins of viviparity in squamates (Jiang et al., 2023; Pyron  
142 & Burbrink, 2014) and reversals back to oviparity (de Fraipont et al., 1996; Fenwick et al., 2011;  
143 Harrington & Reeder, 2017; Lee & Shine, 1998; Pyron & Burbrink; Recknagel et al., 2018).



144 *Saiphos equalis* proved the possibility of reversals when a viviparous individual oviposited an  
145 egg prior to birthing fully developed young within the same litter (Laird et al., 2019). The  
146 unusual absence of an egg-tooth in oviparous Arabian Sand Boas, *Eryx jayakari* (Lynch &  
147 Wagner, 2010; Staub & Emberton, 2002) serves as additional biological evidence of a reversal,  
148 though this has been challenged (Griffith et al., 2015). Importantly, extended embryonic  
149 retention, characteristic of oviparous squamates compared to birds, is viewed as compatible with  
150 labile transitions (Jiang et al., 2023). Current expectations are that oviparity may re-evolve more  
151 easily in squamate lineages that recently evolved viviparity and which have not lost specific  
152 avian eggshell-matrix proteins (Laird et al., 2019; Xie et al., 2022).

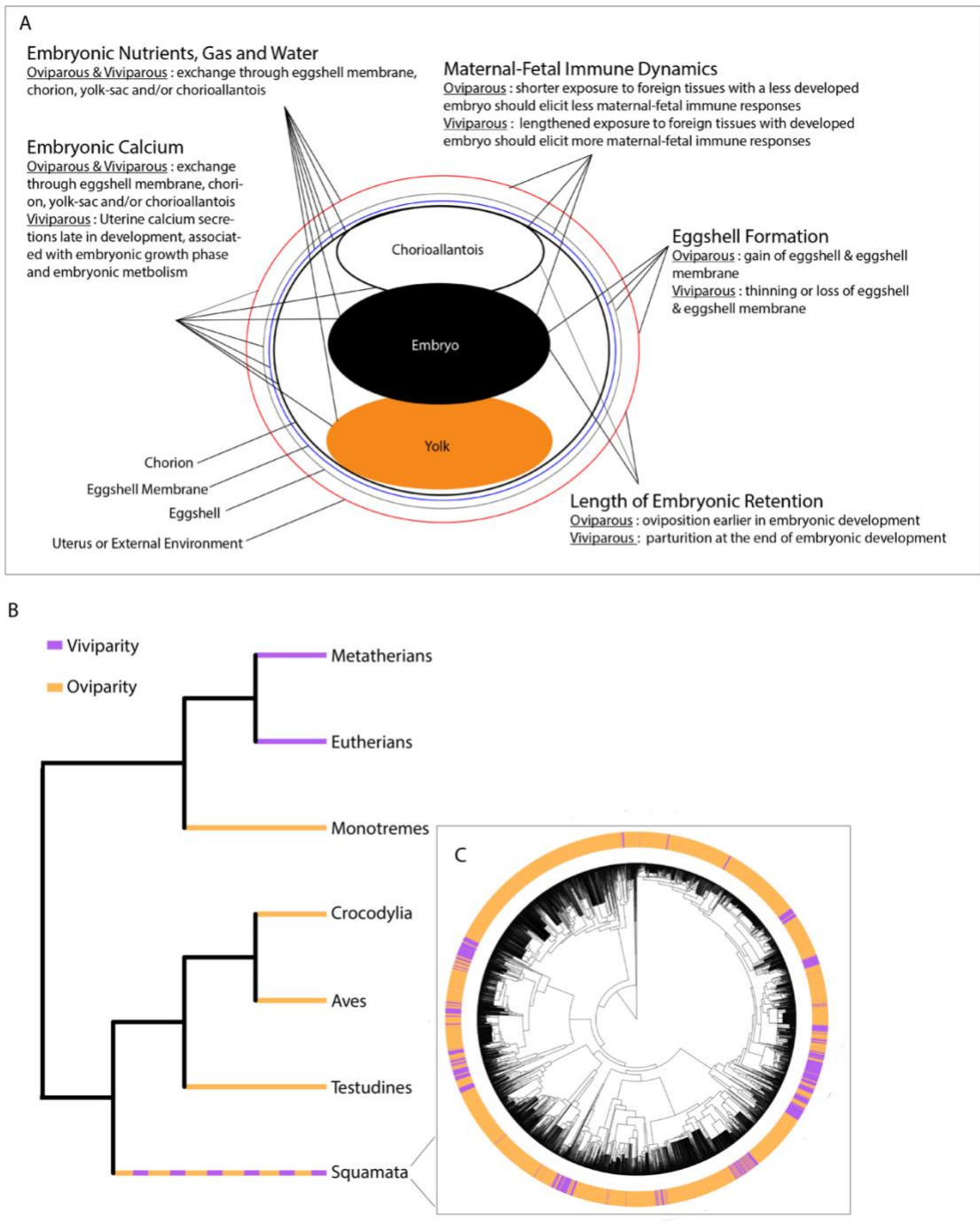
153 Discoveries of viviparity in ancient amniotes are numerous, dating back to the Early  
154 Permian (Chuliver, Scanferla & Smith, 2022; Motani et al., 2014; Piñeiro et al., 2012; Jian et al.,  
155 2023). A viviparous last common ancestor of amniotes may not be unreasonable. A compelling  
156 example is the report that *Ikechosaurus sp.*, a basal archosauromorph, that reached an articulated  
157 stage of embryonic development inside of a parchment shelled egg (Jiang et al., 2023). This and  
158 the ancestral state reconstruction generated in the study bring support to the extended embryonic  
159 retention model (EER) of amniotes origins (Jiang et al., 2023; Hubrecht, 1910). The EER model  
160 postulates that amniote fetal membranes arose through pressure to support exposure to maternal-  
161 fetal tissues during extended embryonic retention (see Laurin et al., 2005 for a summary of  
162 earlier ancestral reconstructions of EER). As Romer (1957) phrased it “It was the egg which  
163 came ashore first; the adult followed”. This is consistent with EER, which is compatible with  
164 both oviparity and viviparity (Laurin, 2005; Mossman 1987). Throughout this review,  
165 considering viviparity as the most extreme form of extended embryonic retention, I hope to  
166 persuade readers to consider the EER model in a new light. I lay this out through a testable

167 hypothesis on the ancestral eggshell of amniotes and Lepidosaurs that can be extended to  
168 amniotes (section III.3), a phylogenetic framework to infer ancestral states based on mechanisms  
169 of maternal-embryonic calcium provisioning (section V.2), and evolutionary pathways that may  
170 support transitions between parity modes (section VII.6 and VII.7).

171         It is sensible to equate the EER with pre-adaptations of the egg to land. Without  
172 substantial amounts of water, converting yolk nutrients to somatic tissue is impossible  
173 (Thompson & Speake, 2003). Water is the primary resource provisioned by the mother of  
174 viviparous squamates and it is stored in extraembryonic membranes (Lourdais et al., 2015). For  
175 example, improper water and gas exchange are associated with poor chorioallantoic blood flow  
176 (Wootton et al., 1977). In oviparous *Saiphos equalis*, a species with extended embryonic  
177 retention, the chorioallantois thickens to support embryonic growth in late development (Parker  
178 et al., 2010). If the amniote egg evolved via the EER model, it may have prompted the origin of  
179 extraembryonic membranes of amniotes to support embryonic water uptake despite the deficit of  
180 water in utero compared to an aqueous environment. This translates to an egg washed ashore that  
181 already evolved to withstand dryer environments.

182         Although models that restrict parity mode evolution to be unidirectional (from oviparity  
183 to viviparity) are shown to be poor fits for squamates (Pyron & Burbrink; Recknagel et al.,  
184 2021b), there is resistance to the proposition that viviparity originated early in Squamata (e.g.  
185 Griffith et al., 2015). The most recent ancestral state reconstruction, built from biomineralization  
186 and parity mode data across 80 extinct and extant amniotes using a single structured Markov  
187 model, inferred viviparity with extended embryonic retention in the first amniotes and in the  
188 most recent common ancestor of Lepidosaurs (squamates and sphenodontians) (Jiang et al.,  
189 2023). However, maximum parsimony, and alternative maximum likelihood and Bayesian

190 reconstructions did not estimate viviparity in the most recent common ancestor of Lepidosaurus  
 191 (Jiang et al., 2023). A testable hypothesis regarding a molecular mechanism that may have  
 192 supported a transition to viviparity at the base of squamates and extended embryonic retention at  
 193 the base of amniotes will help conclude these decades long debates.



194

195 **Figure 1:** Schematic demonstrating (A) the anticipated processes that change during transitions  
196 between oviparity and viviparity, and the organs associated with those changes. Lines from the  
197 process to different organs indicate the organs expected to be involved with the evolutionary  
198 shift between oviparous and viviparous phenotypes. (B) relationships between major amniote  
199 clades and their associated reproductive mode, and (C) the variation of reproductive modes  
200 across squamates. The squamate phylogeny is adapted from Pyron et al., (2016) and reproductive  
201 modes of squamate species from Pyron & Burbrink (2014).

202

203         The ecological drivers of parity mode evolution are beyond the scope of this review.  
204 However, it is generally proposed that viviparity increases protection from adverse  
205 environmental conditions (Ma et al., 2018; Pincheira-Donoso et al., 2017), and a general trend  
206 that supports this is the higher frequency of viviparous squamates, relative to oviparous,  
207 observed at increasing distances from the equator. The cold-climate hypothesis suggests that  
208 viviparity is an adaptation to cold climates, and this is generally accepted by the scientific  
209 community (e.g. Ma et al., 2018; Zimin et al., 2022). Consistent with the cold-climate  
210 hypothesis, a recent study that utilized 65 million years of global paleoclimate data, squamate  
211 phylogeny and parity data for over 3,000 taxa showed that persistent, stable cold climates are  
212 correlated with transitions to viviparity (Recknagel et al., 2021b). Less focus has been on the  
213 adaptive nature of oviparity. Compared to viviparity, oviparity is associated with higher  
214 fecundity and lessened maternal investment (Recknagel et al., 2019).

215         With a deep review of interdisciplinary literature across amniotes and associated  
216 supplementary materials, I explore genomic and physiological features of gestation and  
217 gravidity, including those that could be exploited to support labile shifts, ancestral viviparous

218 states in amniotes and squamates, and those that may facilitate or impede reversals. I propose the  
219 framework of the basal cap hypothesis to help elucidate the ancestral parity modes of squamates  
220 and amniotes. It details how squamates may have transitioned to viviparity (an extreme form of  
221 extended embryonic retention) early in their evolutionary history. I advocate for using squamates  
222 as a model to understand the ancestral state of the amniote egg. Future work should consider this  
223 thoughtfully and embrace the complexity of the system. I hope this manuscript serves as a  
224 foundation for further research on the evolutionary history of the amniote egg and reproductive  
225 mode evolution.

226

227 *(1) Terminology*

228 I use the conventional definition of viviparity as retention of eggs until the stage when the  
229 embryo is fully developed (Blackburn & Stewart, 2021; van Dyke et al., 2014). Oviparity is  
230 defined by eggs that develop outside the mother. I use the terms gravidity and gestation to  
231 describe the period of internal retention of the embryo in oviparous and viviparous taxa,  
232 respectively. Vertebrate placentas are conventionally defined by apposition of maternal and fetal  
233 tissues. It is accepted that all viviparous squamates have a chorioallantoic placenta under this  
234 definition (Blackburn & Stewart, 2021; Stewart & Blackburn, 1988). The avian chorioallantoic  
235 membrane and mammalian chorioallantoic placenta are homologous (Metcalf & Stock, 1993). I  
236 sometimes refer to this organ as the chorioallantoic tissue to describe it for both parity modes.  
237 Oviposition refers to the process and act of egg-laying, while parturition refers to the process and  
238 act of giving birth to live-young. Parition refers to both oviposition and parturition (Blackburn,  
239 1992; Smith, 1975).

240

241 *(1) Main five physiological changes of parity mode transitions*

242 Several physiological features are expected to change during transitions between  
243 oviparity and viviparity (Figure 1). I break this down into five physiological features (hereafter  
244 Main Five)—1) length of embryonic retention (Murphy & Thompson, 2011; Packard et al.,  
245 1977)—only viviparous mothers retain the embryo for the entirety of development; 2) eggshell  
246 formation (Heulin et al., 2005; Packard et al., 1977; van Dyke et al., 2014)—viviparous embryos  
247 generally do not have an eggshell; 3) placental development for maternal-fetal exchange of  
248 required water, gas and/or nutrients (Blackburn, 1992, 2015; Thompson et al., 2000; Thompson  
249 & Speake, 2006); 4) embryonic calcium provisioning (Packard et al., 1985; Shadrix et al., 1994;  
250 Thompson & Speake, 2006)—sources of embryonic calcium and timing of uterine calcium  
251 secretions generally differs between oviparous and viviparous reproduction; 5) maternal-fetal  
252 immune dynamics (e.g., Graham et al., 2011; Hendrawan et al., 2017; Foster et al., 2020)—  
253 viviparous reproduction is associated with maternal and embryonic exposure to foreign tissues,  
254 which is likely to require enhanced regulation of maternal-fetal immune systems.

255

256 **II. Length of Embryonic Retention**

257

258 Viviparous amniotes retain the embryo until it is fully developed, but oviparous amniotes  
259 retain the embryo for a fraction of that time. Rather than using precocious hatching and  
260 parturition (PH&P), like that of opossums and early viviparous mammals (Wagner et al., 2014),  
261 squamates evolve viviparity through extended egg retention (García-Collazo et al., 2012; Shine,  
262 1983). Thus, processes affecting the length of embryonic retention are expected to change to  
263 support transitions between parity modes (van Dyke et al., 2014).

264

265(1) *Parturition & oviposition*

266       The genes and hormones involved with initiating and ending gestation may provide insights  
267 into the tools squamates can co-opt to change the length of embryonic retention during parity  
268 mode transitions. Parturition terminates embryonic retention. Parturition can be divided into four  
269 parts (Terzidou, 2007; Vannuccini et al., 2016)—quiescence (Phase 0), activation (Phase 1),  
270 stimulation (Phase 2) and involution (Phase 3). In eutherian mammals, several processes  
271 contribute to the initiation and termination of gestation including inflammation (Challis et al.,  
272 2009; Hansen et al., 2017), maternal recognition of pregnancy (MRP), mechanical stretch of  
273 uterine tissues (Sooranna et al., 2004; Shynlova et al., 2008), and fluctuating concentrations of  
274 corticotropin-releasing hormone, progesterone, and estrogen (Challis et al., 2000; Condon et al.,  
275 2004; Shaw & Renfree, 2001).

276

277       (i) *Quiescence & sustained progesterone production in reproductive tissues*

278       Extended embryonic retention could be achieved by triggering mechanisms that extend  
279 uterine quiescence, inactivity of the uterus. Inhibition of myometrial contractions through  
280 sustained progesterone production supports quiescence across different viviparous amniotes  
281 (Bazer, 1992; Casey & MacDonald, 1997; Fergusson & Bradshaw, 1991; Ilicic et al., 2017;  
282 Murphy & Thompson, 2011; Putnam et al., 1991; Soloff et al., 2011). The corpus luteum (or  
283 plurally called corpora lutea), a transient progesterone-producing organ, produces progesterone  
284 during gestation. Extended lifespan of the corpus luteum likely aided the evolution of viviparity  
285 in mammals (Amoroso, 1968; Callard et al., 1992; Stouffer & Hennebold, 2015). Thus, early  
286 research on squamate viviparity also explored the influence of corpus luteum lifespan. The

287 lifespan of corpora lutea associates with oviparous egg retention and oviposition (Diaz, Alonso-  
288 Gomez & Delgado, 1994; Fox & Guillette 1987; Jones & Guillette 1982). Eggshell formation in  
289 oviparous Whiptail lizards, *Cnemidophorus uniparens*, is even disrupted by experimental  
290 removal of corpora lutea (Cuellar, 1979). The lifespan of corpora lutea do not consistently  
291 correlate with length of embryonic retention in viviparous squamates like it does in mammals  
292 (Albergotti & Guillette, 2011; Callard et al., 1992).

293 Maternal recognition of pregnancy (MRP) refers to the early signaling of the embryo to  
294 prevent luteolysis (Thatcher, Meyer, & Danet-Desnoyers, 1995), degradation of the corpus  
295 luteum. Luteolysis occurs in the absence of pregnancy. MRP enables continued progesterone  
296 production by the corpus luteum to support uterine quiescence during early gestation. An  
297 independent evolution of MRP is reported for Macropodidae, a lineage of marsupial mammals  
298 (Freyer, Zeller, & Renfree, 2003), and endometrial recognition of pregnancy is recognized in the  
299 opossum (Griffith et al., 2019). MRP has not been explicitly studied in squamates. However,  
300 MRP likely happens in squamates, given that corpora lutea do not get degraded in the earliest  
301 stages of gravidity/gestation in oviparous or viviparous squamates (Callard et al., 1992;  
302 Albergotti & Guillette, 2011).

303 Different genes are signaled by embryos for MRP across mammals. Human chorionic  
304 gonadotropin hormone (hCG) establishes MRP (Ross, 1979; Behrman et al., 1993; Duncan,  
305 McNeilly, & Illingworth, 1998; Duncan, 2000; Ticconi et al., 2007). In pigs, MRP is  
306 hypothesized to be triggered by collaborative signaling of estradiol (E2) and prostaglandins  
307 (PGs) (Geisert et al., 2023). Similarly, glycoproteins, estradiol and prostaglandin E2 (PGE2)  
308 have been implicated in signaling MRP in horses (Klein & Troedsson, 2011; Klein, 2016). In  
309 ruminants, embryonic signaling of IFN- $\tau$  establishes MRP (Bazer, 2013; Bazer, Spencer & Ott,



310 1997; Thatcher et al., 1995). During gestation in the uterus of viviparous African Ocellated  
311 skinks, *Chalcides ocellatus*, four receptors for interferon alpha, beta, omega, and gamma are  
312 differentially expressed but no expression of IFN- $\tau$  was detected compared to non-gestational  
313 uterine tissue (Brandley et al., 2012). I was unable to find expression patterns of MRP signaling  
314 homologs in other squamate reproductive tissues. Should MRP occur in squamates, it may be  
315 signaled by genes that are clade-specific, like in mammals. This makes comparatively evaluating  
316 the influence of MRP on the evolution of viviparity an interesting avenue for future research.

317 The evolution of viviparous extended embryonic retention may be sufficiently supported by  
318 maintenance of chorioallantoic progesterone production coupled with eggshell loss (Griffith,  
319 Brandley et al., 2017). This theory may be broadly applicable across amniotes given that the  
320 most recent common ancestor of amniotes likely had a chorioallantois with an endocrine  
321 function (Griffith, Brandley et al., 2017). Following death of the corpus luteum during gestation,  
322 placental progesterone production supports extended embryonic retention in eutherian mammals  
323 (Castracane & Goldzieher, 1986; Ellinwood et al., 1989; Nakajima et al., 1991; Rothchild, 2003;  
324 Spencer & Bazer, 2004). Viviparous Italian Three-toed Skinks, *Chalcides chalcides*, shift to  
325 chorioallantoic progesterone production following degradation of corpora lutea during gestation  
326 (Guarino et al., 1998). The placenta of viviparous Southern Snow Skinks, *Carinascincus*  
327 *microlepidotus*, produces minimal progesterone but has a strong capacity to convert  
328 pregnenolone to progesterone (Girling & Jones, 2003). Whereas all genes involved with a known  
329 biosynthesis pathway for progesterone production are expressed in the placenta of horses, *Equus*  
330 *caballus*, only some of these genes were detected in the chorioallantois of chickens, *Gallus*  
331 *gallus*, viviparous Southern Grass Skinks, *Pseudemoia entrecasteauxii*, and oviparous and  
332 viviparous Southeastern Sliders, *Lerista bougainvillii* (Griffith, Brandley et al., 2017). Thus, if

333 chorioallantoic progesterone production has supported multiple origins of viviparity in amniotes,  
334 it is not evidenced by a conserved ancestral gene expression pattern for the biosynthesis of  
335 progesterone (Griffith, Brandley et al., 2017). Nonetheless, parity trait genes in a reproductively  
336 bimodal lizard, *Zootoca vivipara*, are associated with progesterone-binding functions (Recknagel  
337 et al., 2021a)—highlighting the role of progesterone in squamate reproduction.

338 Other female reproductive tissues in squamates express genes involved with progesterone  
339 biosynthesis—StAR-related lipid transfer domain protein 3 (*StARD3*) and hydroxy-delta-5-  
340 steroid dehydrogenase (*HSD3B1*). *STARD3* is significantly upregulated in the uterine tissue  
341 during pregnancy in viviparous African Ocellated skinks, *Chalcides ocellatus*, along with  
342 significant differential expression of seven paralogs (Brandley et al., 2012). While *StARD3* is  
343 expressed during gestation in *Zootoca vivipara*, it is not significant differentially expressed  
344 compared to oviparous counterparts; *HSD3B1*, on the other hand, is significantly upregulated  
345 during mid-gestation (Recknagel et al., 2021a). Compared to non-gestational samples, *HSD3B1*  
346 is significantly upregulated in the uterus during early and late gestation in viviparous individuals  
347 of reproductively bimodal *Saiphos equalis* (Foster et al., 2020). Oviparous individuals from the  
348 same species did not exhibit this expression pattern (Foster et al., 2020). Activity of *HSD3B1*  
349 was detected in the mucosal epithelium of oviparous Eastern Garden Lizards, *Calotes versicolor*  
350 (Kumari et al., 1992), and in the uterine glands of oviparous Keeled Indian Mabuya, *Eutropis*  
351 *carinata* (Mundkur & Sarkar, 1982). Other genes involved with the biosynthesis of progesterone  
352 (e.g., steroidogenic acute regulatory protein or cytochrome-P450-family-11-subfamily-A-  
353 polypeptide-1) serve as further candidates for exploring the relationship between organ-specific  
354 patterns of progesterone production and the evolution of extended embryonic retention in  
355 viviparous squamates.

356 For progesterone to prevent myometrial contractions and support quiescence, there must be  
357 progesterone receptors (PGRs) in the uterus (Mesiano et al., 2011; Young et al., 2011). In  
358 humans, progesterone responsiveness is related to specific ratios of PGRs, *PR-A* and *PR-B*, in  
359 myometrial cells (Young et al., 2011). Minimal research exists on PGR expression in squamate  
360 reproductive tissues. One study found that in the uterus of the yolk-sac in viviparous Southern  
361 Grass Skinks, *Pseudemoia entrecasteauxii*, one progesterone receptor, *PGRMC2*, is upregulated  
362 compared to non-gestational uterine tissue (Griffith et al., 2016); Another progesterone receptor,  
363 *PGR*, is downregulated in the uterus of the chorioallantoic placenta and yolk sac placenta  
364 compared to non-gestational uterine tissue (Griffith et al., 2016). Downregulation of both *PGR*  
365 and *PGRMC2* in the uterus during gestation was detected in viviparous *Chalcides ocellatus*  
366 (Brandley et al., 2012). While *PGR* is differentially expressed at mid-gestation in viviparous  
367 individuals compared to oviparous, *PGRMC1* and *PGRMC2* are not differentially expressed  
368 (Recknagel et al., 2021a). However, admixture mapping revealed three SNPs most highly  
369 associated with gestation length in *Zootoca vivipara* are located in close proximity to *PGRMC1*  
370 (Recknagel et al, 2021a). Measuring expression of PGRs and their ratios in uteruses of  
371 oviparous and viviparous squamates will help elucidate the receptors needed to support  
372 progesterone responsiveness in squamate uteruses and their relationship to extended embryonic  
373 retention.

374

375 (ii) *Activation & progesterone withdrawal*

376 The activation stage of parturition is marked by the withdrawal, or functional withdrawal, of  
377 progesterone leading to an estrogen dominated response during the next state, stimulation  
378 (Bakker, Pierce, & Myers, 2017; Fergusson & Bradshaw, 1991). Progesterone may withdraw in

379 response to environmental stimuli in reptiles during parturition (Shine & Guillette, 1988). In  
380 mammals, activation is marked by increasing concentrations of corticotropin-releasing hormone  
381 and contraction associated proteins (CAPs) including connexin-43, prostaglandins, oxytocin  
382 receptors, prostanoid receptors and cell signaling proteins (Bakker et al., 2017; Ilicic et al., 2017;  
383 Leadon et al., 1982; Pashen & Allen, 1979; Whittle et al., 2000). Pro-inflammatory cytokines  
384 and chemokines, prostaglandin synthase-2 (*COX-2*, also referred to as *PTGS2*), and NF- $\kappa$ B also  
385 influence activation in mammals (Christiaens et al., 2008; Lappas et al., 2002; Lappas & Rice,  
386 2007; Lindström & Bennett, 2005; Olson, 2003; Terzidou, 2007).

387 Some similar patterns are associated with oviposition in birds. In chickens, *Gallus gallus*,  
388 prostaglandin F (PGF) concentrations increase in the hours leading up to oviposition (Takahashi  
389 et al., 2004). Experimental injection of oxytocin and arginine vasotocin (AVT), similar  
390 neurohypophyseal peptides, revealed that uterine tissues of chickens, *Gallus gallus*, maintain  
391 responsiveness to oxytocin but are more sensitive toward arginine vasotocin (Ewy, 1970).  
392 Murphy & Thompson (2011) provide a rather exhaustive list of resources on progesterone and  
393 estrogen assays across oviparous and viviparous squamates. Future research should consider  
394 exploring parallels between mechanisms of activation in mammals and squamates. Any process  
395 that can trigger or stall activation should lead to extended embryonic retention.

396

397 (iii) *Stimulation & electrical gradients, inflammation, and hormonal regulation*

398 Mechanical stretch, electrical gradients, inflammatory processes, and hormonal regulation  
399 contribute to stimulation, the phase when contractions, cervical ripening and dilation occur.  
400 Stimulation involves contributions from maternal and fetal tissues. As early as 460 BC there was  
401 uncertainty over the proportional influence of mother or fetus on the initiation of parturition.

402 Hippocrates proposed that the fetus initiates parturition by pushing its feet on the fundus of the  
403 uterus. Although the reality is not so cartoonish, mechanical stretch of the uterus from the  
404 growing embryo plays a role in parturition (Lefebvre et al., 1995; Tamizian & Arulkumaran,  
405 2004; Wray et al., 2015).

406 Physical stretching of the uterus causes an influx of calcium and sodium, altering the action  
407 potential and enabling contractions (Kao & McCullough, 1975). Calcium further activates  
408 voltage gated calcium channels on myometrial cell membranes, enhancing the influx of calcium  
409 ions, mediating the force and speed of myometrial contractility (Arrowsmith & Wray, 2014;  
410 Wray et al., 2015). The influence of uterine overdistention on parition in birds and non-avian  
411 reptiles has not yet been examined, to my knowledge. However, differentially expressed genes  
412 functionally enriched the GO term for “voltage-gated calcium channel activity” in uterine tissues  
413 during gravidity and gestation in *Saiphos equalis* (Foster et al., 2020). A uterine response to  
414 overdistention is among the many possible explanations for this. It may be important to consider  
415 the influence of uterine overdistention on squamate parity mode transitions, because should  
416 bioelectrical responses to uterine overdistention be a common feature of vertebrate parturition,  
417 lessened distention may be a hurdle to reverse back to oviparity. Uterine overdistention may  
418 influence parturition by triggering an “inflammatory pulse” that activates further myometrial  
419 contractility, which leads to preterm birth in primates (Adams Waldorf et al., 2015).

420 During parturition, there is an influx of uterine and embryonic pro-inflammatory genes and  
421 immune cells (Adams Waldorf et al., 2015; Charpigny et al., 2003; Mesiano et al., 2002; Park et  
422 al., 2005). Uterine contractions in humans involve actions of prostaglandins (PGs), oxytocin,  
423 corticotropin-releasing hormone, cytokines, and neutrophils (Adams Waldorf et al., 2015; De

424 Rensis et al., 2012; Olson & Hertelendy, 1983; Park et al., 2005; Sykes et al., 2014; Terzidou,  
425 2007).

426 The cycling concentrations of a neuropeptide, corticotropin-releasing hormone (CRH),  
427 supports parturition in humans. This has been compared to a biological clock that is initiated at  
428 early stages of gestation (Lockwood, 2004; McLean & Smith, 2001). Increased production of  
429 CRH facilitates parturition by interacting with CRH receptors, CRH-R1 and CRH-R2, which are  
430 suggested to promote myometrial relaxation or contractility, respectively (Hillhouse &  
431 Grammatopoulos, 2001). Altered regulation, phenotype or function of hormones that function as  
432 biological clocks, like CRH, may have a particularly strong influence on evolutionary changes to  
433 length of embryonic retention, a trait inherently related to time.

434 Placental CRH production has only been identified in primates thus far (Challis et al., 2005;  
435 Emanuel et al., 1994; Florio et al., 2002; Hillhouse & Grammatopoulos, 2001; Karteris et al.,  
436 1998; Mendelson, 2009; Robinson et al., 1989). Placental CRH production may, therefore, be  
437 unique to primates. However, the amino acid sequence of CRH is highly conserved in vertebrates  
438 (Noy et al., 2017), indicating there is a possibility for shared function across diverse taxa. Like  
439 CRH cycling in mammals, timely fluctuations of AVT stimulates uterine contractions, enables  
440 oviposition in birds, turtles, and lizards (Ewy, 1970; Fergusson & Bradshaw, 1991; Guillette Jr &  
441 Jones, 1980; Jones et al., 1987; Rzas, 1978; Wu et al., 2019).

442 Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) influence, respectively, uterine  
443 contractions and cervical relaxation for partition across many amniotes including humans, *Homo*  
444 *sapiens* (Terzidou, 2007), domestic pigs (De Rensis et al. 2012), domestic chickens (Hertelendy  
445 et al., 1974; Olson et al., 1986), and Loggerhead Sea turtles (Guillette et al., 1991). Injections of  
446 PGF<sub>2α</sub> and PGE<sub>2</sub> induce parturition in viviparous Yarrow's Spiny lizards, *Sceloporus jarrovi*, and

447 Raukawa geckos, *Woodworthia maculatus* (Cree & Guillette, 1991; Guillette et al., 1992).  
448 However, no injected dosages of PGF<sub>2α</sub> or PGE<sub>2</sub> induced oviposition in oviparous Collard  
449 lizards, *Crotaphytus collaris*, Eastern Fence lizards, *Sceloporus undulatus*, Six-lined  
450 racerunners, *Aspidoscelis sexlineatus*, or Striped Plateau lizards, *Sceloporus virgatus* (Guillette et  
451 al., 1991). It is interesting that injections of PGF<sub>2α</sub> and PGE<sub>2</sub> induced parturition in viviparous  
452 lizards but did not induce oviposition in oviparous lizards studied. Given this, it is plausible that  
453 regulatory or functional changes to PGF<sub>2α</sub> and/or PGE<sub>2</sub> in squamates could facilitate changes to  
454 the length of embryonic retention to support transitions between reproductive modes. However,  
455 induction of parturition with PGF<sub>2α</sub> in viviparous *Woodworthia maculatus* only worked with  
456 pre-treatment of β-adrenoceptor (Cree & Guillette, 1991).

457 PGF<sub>2α</sub> decreases progesterone concentrations during stimulation (De Rensis et al., 2012). In  
458 humans, biosynthesis of PGs is driven largely by the enzyme cyclooxygenase (*COX*)-2 rather  
459 than *COX-1* (i.e., prostaglandin synthase-2 and -1) (Slater et al., 1995, 1999). This helps  
460 maintain the decreased progesterone/estrogen ratio of stimulation. In ovariectomize viviparous  
461 Garter snakes, *Thamnophis*, increased estrogen stimulated thickness of uterine epithelial cells  
462 and glandular activity, whereas administration of progesterone had little influence on uterine  
463 histology (Mead et al., 1981). Uterine pig models revealed that estrogen stimulates involuntary  
464 contraction and relaxation (peristalsis) of the uterus (Mueller et al., 2006).

465 The softening of the cervix is important during the stimulation stage of parturition. A  
466 hormone related to insulin, *relaxin*, promotes myometrial softening in humans, *Homo sapiens*,  
467 domestic pigs, and turtles (Mercado-Simmen et al., 1982; Sorbera et al., 1988; Weiss &  
468 Goldsmith, 2001). The cervix also gets softer by actions of PGE<sub>2</sub>. PGE<sub>2</sub> activates pro-  
469 inflammatory cytokines, interleukin (IL)-8 and tumor necrosis factor (TNF)-α, which activates

470 the collagenases and matrix metalloproteinases for cervical softening (Bakker et al., 2017). This  
471 causes a positive feedback loop between IL-8 and PGE<sub>2</sub> synthesis (Denison et al., 1998;  
472 Denison, Calder & Kelly, 1999; Terzidou, 2007; Li et al., 2010). Upregulated of IL-8 is also  
473 promoted by the protein complex NF-κB during parturition in humans (Elliott, 2001). Similar  
474 patterns were observed during parturition in mice and baboons (Mendelson & Condon, 2005;  
475 Mendelson, 2009).

476 A few studies focus on the role of cytokines on squamate reproduction but not explicitly  
477 during oviposition or parturition (Hendrawan et al., 2017; Paulesu et al., 1995, 2005, 2008).  
478 Some studies detected expression of cytokines during late gestation (Foster et al., 2020; Gao et  
479 al., 2019; Recknagel et al., 2021a). TNF-α related activity was only detected at this time in  
480 viviparous Tussock Cool-skinks, *Pseudemoia entrecasteauxii*, which were found to  
481 downregulate TNF-α induced proteins (*TNFAIP6* and *TNFAIP8L2*) in the ‘uterus of the  
482 chorioallantoic placenta’ and *TNFAIP6*, *TNFAIP1*, and *TNFAIP2* in the ‘uterus of the yolk-sac  
483 placenta’ compared to not gestational uterine tissues (Griffith et al., 2016). Activity of TNF-α in  
484 reproductive tissues during gestation in viviparous Italian Three-toed skinks, *Chalcides*  
485 *chalcides*, and reproductively bimodal European common lizards, *Zootoca vivipara*, was  
486 associated with maternal-fetal immune dynamics (Paulesu et al., 1995, 2005, 2008; Hendrawan  
487 et al., 2017).

488 Altered expression or phenotype of contractility agonists, oxytocin receptors and estrogen  
489 receptors, and contractility antagonists, progesterone receptors and β-adrenergic receptors  
490 (Ravanos et al., 2015) may also change the length of embryonic retention to support transitions  
491 between parity modes. Differences in length of embryonic retention in oviparous and viviparous  
492 agamas, *Phrynocephalus przewalskii* and *Phrynocephalus vlangalii*, appears to be driven by



493 regulatory differences of prostaglandins, *COX-2*, an AVT receptor (*MTR*),  $\beta$ -adrenergic receptors,  
494 and estrogen receptors. During oviposition, *P. przewalskii*, exhibited the following: promotion of  
495 contractions through downregulation of  $\beta$ -adrenergic receptor (*ADRB2*), and upregulation of  
496 *COX-2* and prostaglandin, and absent (potentially lost) expression of two estrogen receptors  
497 (*ESR1* and *ESR2*) and the AVT receptor, *MTR* (Gao et al., 2019). During the stage of gestation  
498 corresponding to oviposition, viviparous sister-species, *P. vlangalii*, exhibited the following  
499 alternate pattern: inhibition of contractions caused by upregulation of *ADRB2* and  
500 downregulation of two estrogen receptors (*ESR1*, *ESR2*), *MTR*, *COX-2*, and prostaglandin (Gao  
501 et al., 2019). Some viviparous squamates, *Saiphos equalis*, *Chalcides ocellatus*, and *Pseudemoia*  
502 *entrecasteauxii*, share some of these expression patterns (*COX-2*, *MTR*, and *ADRB*, respectively)  
503 thought to be involved with extended embryonic retention in viviparous *P. vlangalii* (Brandley et  
504 al., 2012; Foster et al., 2020; Gao et al., 2019; Griffith et al., 2016); and *ADRB2* is upregulated at  
505 mid-gestation in viviparous *Zootoca vivipara* compared to oviparous counterpart (Recknagel et  
506 al., 2021a). Overexpressed genes in viviparous uterine tissues of *Zootoca vivipara* also  
507 functionally enriched pathways for beta 1 and beta 2 adrenergic receptor signaling pathways  
508 (Recknagel et al., 2021a). This study, which compared uterine expression profiles during  
509 gestation across viviparous species of squamates, rodents, canines, ungulates, and humans,  
510 concluded that shared regulatory networks are recruited to support viviparity (Reckangel et al.,  
511 2021a).

512 Recently, in humans, the only Classical Major Histocompatibility Antigen (C-MHC)  
513 expressed by trophoblasts (specialized placental cells) was associated with parturition when it  
514 was discovered that HLA-C is significantly increased during laboring term and preterm placentas  
515 compared to non-laboring placentas (Hackmon et al., 2017). The authors suggested a mechanism

516 where fetal HLA-C open conformers on the placenta provoke inflammation of maternal tissues,  
517 leading to parturition (Hackmon et al., 2017). Expression of MHC alloantigens, foreign antigens  
518 to the host, by fetal cells is also associated with parturition in cows and horses (Benedictusa,  
519 Koets & Ruttena, 2015; Davies et al., 2004; Joosten et al., 1991; Rapacz-Leonard et al., 2018).  
520 Around one month prior to parturition in cows, endometrial epithelium thins and eventually  
521 disappears completely, putting the antigen-presenting trophoblasts (Adams et al., 2007) in  
522 contact with maternal connective tissue of the endometrium (Podhalicz-Dzięgielewska et al.,  
523 2000). Fetal MHC alloantigens are proposed to promote the loosening of maternal and fetal  
524 tissues (Benedictusa et al., 2015). MHC molecules are expressed during gestation in some  
525 squamates (Murphy, Thompson & Belov, 2009) but their role in oviposition or parturition has  
526 not yet been considered to my knowledge. Identifying the presence or absence of MHC  
527 alloantigens on embryonic tissues before and during partition across more diverse taxa may  
528 reveal how ubiquitous the influence of embryonic MHC molecules is on this.

529       Involution (phase 3) occurs after the embryo(s) is released. In eutherian involution, the  
530 placenta detaches, and the uterus shrinks. This is supported by actions of prostaglandins  
531 (Husslein, 1984) and oxytocin (Terzidou, 2007). It seems unlikely for processes of involution to  
532 be related to evolutionary changes to the length of embryonic retention.

533

#### 534       (2) *Unique qualities of oviposition & parturition in Sauropsids*

535       The physiology of avian oviposition is dependent on a circadian schedule (Williams, 2012).  
536 A general model of an “open period”, when eggs are laid are separated by “laying gaps”  
537 (Williams, 2012). Chicken ovulation and oviposition cycles leave an 8-hour open period where  
538 luteinizing hormone (LH) and progesterone surge, initiating ovulation and continuing the cycle.

539 At the extreme, the ancient murrelet, *Synthliboramphus antiquus*, oviposits a two-egg clutch on  
540 seven-day intervals (Williams, 2012). Longer laying intervals have been associated with longer  
541 intervals between initiation of yolk development (Astheimer & Grau, 1990). Differing from  
542 birds, oviparous squamates retain eggs longer than the ovarian cycle (Tinkle & Gibbons, 1977).  
543 This suggests that oviparous squamates may rely on different molecular mechanisms to support  
544 oviposition than birds.

545 Non-avian reptiles are unique in that they are the only ectothermic amniotes. This makes  
546 them uniquely reliant on temperature for embryonic retention and associated embryonic  
547 signaling to indicate the stage of embryonic development. Additionally unique, gemales are the  
548 heterogametic sex in several squamates, leading some research to suggest chromosome linkage  
549 evolution may increase the speed of evolution in genes associated with gestation length  
550 (Recknagel et al., 2021a). Admixture mapping, made possible by the natural hybridization of  
551 oviparous and viviparous populations of *Zootoca vivipara*, revealed 439 candidate genes  
552 associated with embryonic retention (Recknagel et al., 2021a). Eleven of these genes were also  
553 associated with eggshell traits (Recknagel et al., 2021a)—underscoring the pleiotropic roles of  
554 some genes putatively involved in squamate parity mode evolution.

555

### 556(3) *Pre-term birth & embryonic retention mechanisms*

557 The literature on pre-term birth may be a fruitful avenue of research to inform understanding  
558 on the evolutionary genomics of embryonic retention length. Slower increases of CRH (Ellis et  
559 al., 2002) and higher expression of Neurokinin B, for example, are associated with pre-term birth  
560 in humans (Torricelli et al., 2007). Injections of RU486, a progesterone receptor (PGR)  
561 antagonist, promoted pre-term labor in rhesus macaques but the progression of physiological

562 activity differed from normal parturition (Haluska et al., 1987). Examining homologs of genes  
563 involved with human pre-term birth in squamates may provide further candidates for genes that  
564 could impact the length of embryonic retention in squamates. Some evolutionary studies are  
565 taking implications of pre-term birth into account. For example, a comparative evolutionary  
566 transcriptomics study across therians, monotremes, squamates, and an amphibian recently  
567 associated *HAND2* with preterm birth in Eutherian mammals (Marinić et al., 2021).

568 In humans, pregnancy loss from infection follows distorted ratios of immune factors at the  
569 maternal-fetal interface (Arenas-Hernandez et al., 2016; Chaturvedi et al., 2015; Chattopadhyay  
570 et al., 2010). Future research on the evolution of lengthened embryonic retention to support  
571 viviparity may benefit from exploring ratios of immune cells in the uterus and embryonic tissues  
572 during term and pre-term pregnancy in squamates. I direct researchers to the literature on the  
573 reptile immune system and immune cell ratios at the maternal fetal interface during term and pre-  
574 term mammalian pregnancy for further exploration (Yang et al., 2019; Zimmerman, 2010, 2020).

575

#### 576(4) *Discussion & future directions—embryonic retention and parity mode evolution*

577 The physiological processes involved with the start of gestation (maternal recognition of  
578 pregnancy) and the end of gestation (partition) in birds and mammals provide insights into the  
579 genes and hormones squamates may co-opt to alter length of embryonic retention during  
580 transitions between parity modes. Unsurprisingly, hormones like estrogen and progesterone, play  
581 important roles in partition across amniotes. Further processes to be examined in squamates  
582 include signaling of homologous genes for MRP, placental progesterone production, novel  
583 pathways for biosynthesis of progesterone, the role of beta 1 and beta 2 adrenergic receptor  
584 signaling pathways, fluctuating ratios of progesterone receptors, the lifespan of the corpus

585 luteum across a broader range of taxa, production and circulation of homologs for AVT and  
586 CRH or other similarly structured genes, expression of fetal alloantigens and inflammatory  
587 cytokines in utero, and the influence of uterine overdistention on contractions. Regarding  
588 squamate parity mode transitions, the role of uterine overdistention in mammalian parturition  
589 suggests a lack of uterine overdistention may be one hurdle for reversals back to oviparity.  
590 Understanding the evolutionary physiology and genomics of embryonic retention in oviparous  
591 and viviparous squamates will benefit from focused attention on reproductively bimodal species  
592 (Whittington et al., 2022) and from genomics/physiological research across more taxa that vary  
593 in reproductive modes.

594

### 595 **III. Eggshell Formation**

596

597 Oviparous amniotic embryos develop within an eggshell that is at least partially  
598 mineralized, whereas viviparous embryos generally do not. Primarily, the eggshell serves as  
599 physical protection and calcium reserve (Stewart & Ecy 2010; Stewart et al., 2009). The  
600 eggshell matrix contains immune properties and pores that enable gas exchange and water uptake  
601 (Packard et al., 1982). Evolutionary transitions between parity modes therefore requires changes  
602 to the process of eggshell formation. The history of research on the evolutionary morphology of  
603 the amniote egg is important for future comparative research (Blackburn & Stewart, 2021). Some  
604 have suggested that the amniote eggshell originated multiple times (Aoki, 1993).

605 Birds have hard calcareous eggshells. Other than two lineages of geckos with hard shells,  
606 oviparous squamates have parchment-shelled eggs with a thin layer of calcium deposits on the  
607 outer surface of the shell membrane (Blackburn & Stewart, 2021; Choi et al., 2018).

608 Monotremata (egg-laying mammals) have an eggshell but far less has been documented about its  
609 structure compared to other amniotes (Legendre et al., 2022). The structure and physiological  
610 mechanisms involved with eggshell calcification are most well resolved in birds (Choi et al.,  
611 2018; Francesch et al., 1997; Jonchère et al., 2010, 2012; Rose-Martel, Du, & Hincke, 2012).  
612 Eggshell deposition in tuatara and squamates differs dramatically (Choi et al., 2018). Viviparous  
613 squamates lack an eggshell, absorb the eggshell during gestation, or have a thin layer of calcium  
614 deposits.

615         The earliest records of amniote eggshells have features characteristics of Archelosaur  
616 eggshells, including the mammillary layer (Stein et al., 2019; Legendre et al., 2022). Recent  
617 reconstructions are consistent with a thin eggshell in ancestral dinosaurs (Norell et al., 2020;  
618 Stein et al., 2019). It is important to consider that the semi-rigid shells of Lepidosaur and  
619 testudines are not homologous (Legendre et al., 2022); the microstructure of Archelosauria  
620 (birds, crocodiles, turtles and dinosaurs) and Lepidosaur eggshells are remarkably different (Choi  
621 et al., 2018); and recent reconstructions of the composition and ultrastructure of dinosaur  
622 eggshells revealed that calcified hard eggshell of dinosaurs originated three times (Norell et al.,  
623 2020). In the remainder of this section, I consider how structural, mineral,  
624 genomic/transcriptomic, and proteomic information on amniote eggshells can inform scientific  
625 understanding of the ancestral eggshell of amniotes and Lepidosaur.

626         The genetic drivers of eggshell formation are not resolved in squamates. Two oviparous  
627 lizards, *Lerista bougainvillii* and *Lampropholis guichenoti*, differentially express either zero or  
628 two genes, respectively, in utero in non-gravid vs gravid comparisons (Griffith et al., 2016).  
629 However, this study only measured gene expression at one developmental stage, making it  
630 difficult to infer if regulatory changes influence eggshell formation. Nonetheless, oviparous

631 *Saiphos equalis* and *Phrynocephalus przewalskii* have extensive differential expression during  
632 gravidity (Foster et al., 2020; Gao et al 2019). It is interesting to see drastically different uterine  
633 gene expression profiles associated with oviparity, given that shared genes are recruited to the  
634 uterus to support viviparity across diverse amniotes (Recknagel et al., 2021a). Under the  
635 assumption that conserved traits should be accompanied with more similar gene expression  
636 profiles than convergent traits, uterine gene expression profiles in themselves currently reveal  
637 more conserved regulatory networks in utero for squamate viviparity than oviparity.

638         Some genetically determined traits are known to be evolutionarily labile in squamates, like  
639 venom and limb reduction (Camaiti et al., 2021; Sites et al., 2011). In *Saiphos equalis*, shell  
640 characteristics of facultatively partitioned oviparous and viviparous embryos are similar, leading  
641 authors to infer that both parity modes utilize the same machinery to produce egg coverings  
642 (Laird et al., 2019). In this species, environmental influences on gestation length, rather than  
643 genetic influences on eggshell thickness, may play a more dominant role in parity mode  
644 evolution (Laird et al., 2019). In *Zootoca vivipara*, Recknagel et al. (2021a) identified 38  
645 candidate genes associated with eggshell traits and concluded that the genetic architecture of  
646 eggshell traits is simpler than that of gestation length.

647

#### 648         (1) *Mineral composition of eggshells*

649         The different mineral compositions of eggshells across amniotes may provide insight into the  
650 differing physiological conditions and evolutionary histories under which they are formed (Table  
651 1). Taxa use a polymorph of calcium carbonate—calcite, aragonite or vaterite—to develop the  
652 eggshell (Hincke et al., 2012). Amorphous calcium carbonate (ACC) is a transient non-  
653 crystalline precursor phase of calcite and aragonite that is important for many calcification

654 processes in invertebrates (Hincke et al., 2012). It was recently shown to control avian eggshell  
 655 mineralization (Rodríguez-Navarro et al., 2015).

656 In birds, the organic components of uterine fluid promote the formation of calcite  
 657 (Hernández-Hernández, Gomez-Morales et al., 2008; Hernández-Hernández, Rodriguez, et al.,  
 658 2008; Hernández-Hernández, Vidal et al., 2008). Most amniotes use this polymorph (Hernández-  
 659 Hernández, Gomez-Morales et al., 2008; Hernández-Hernández, Rodriguez, et al., 2008;  
 660 Legendre et al., 2022). However, turtle eggshells are predominately developed with aragonite  
 661 (Choi et al., 2022; Mikhailov, 1997). The eggshell of most squamates consists of an inner fibrous  
 662 protein layer overlain by calcium carbonate that can be a single layer or scattered crystals (Choi  
 663 et al., 2018; Packard & DeMarco, 1991; Stewart et al., 2010).

664 There are differing accounts on the microstructure of monotreme eggshells, however  
 665 conceptus coats include three layers including zona pellucida, mocooid coat and shell coat  
 666 (Frankenberg & Renfree, 2018). Further studies are needed test for secondary homology.  
 667 Monotreme shells are described as proteinaceous, permeable, and flexible (Hughes, 1984).  
 668 Marsupials lack an eggshell but have an eggshell coat, similar to that of monotremes  
 669 (Frankenberg & Renfree, 2018), that is secreted by the epithelial cells and endometrial glands  
 670 early on in embryonic development prior to implantation (Roberts et al., 1994; Roberts & Breed,  
 671 1996). Upon hatching of the shell coat and attachment of the embryo, a cooperative  
 672 inflammatory response ensues (Stadtmauer et al., 2020a, 2020b).

673 **Table 1.** Amniote Eggshell Ultrastructures

Taxon	Eggshell ultrastructure
Testudoid	Radial aragonite with organic core at base
Crocodiloid	Tabular, arranged in wedges of calcite with no organic core
Squamate	Two types: <ul style="list-style-type: none"> <li>• rigid-shelled eggs with well-developed crystalline layer (dibamid and gekkonid lizards). Stem-like crystals grow downward making for a rigid shell</li> <li>• flexible-shelled eggs with parchment-like shell of fibrils overlaid with little thin crystal caps or no crystalline material (other squamates)</li> </ul>



Ornithoid (avian)	Calcite with a clear boundary between lower and upper parts. Mammillary layer defines the lower portion of the shell, with calcite crystals that radiate upwards
Monotreme	Distensible, permeable and highly proteinaceous

674 Note: Adapted from Choi et al., (2018); Frankenberg & Renfree, (2018); Hallman & Griebeler, (2015); Hincke et  
675 al., (2012); Trauth & Fagerberg, (1984)

676

677

678 (2) *Uterine glands & the evolution of parity modes*

679 Eggshell formation occurs in the uterus where the uterine glands secrete precursors of the  
680 eggshell (Girling, 2002; Guillette, Fox & Palmer, 1989; Jonchère et al., 2010; Nys et al., 2004;  
681 Picariello et al., 1989; Stewart & Eca, 2010). Uterine glands are critical for gravidity/gestation  
682 in both oviparous and viviparous amniotes (Braz et al., 2018; Burton et al., 2002; Cooke et al.,  
683 2013). For example, in humans, uterine glands provide histiotrophic nutrition to the early  
684 embryo (Burton et al., 2002). In reptiles, precursors for the proteinaceous eggshell membrane are  
685 secreted by the uterine glands (Corso, Delitala & Carcupino, 2000; Heulin et al., 2005; Palmer et  
686 al., 1993). Calcium secretion can also involve uterine epithelial cells (Herbert, Thompson &  
687 Lindsay, 2006; Thompson et al., 2007). Uterine epithelium of the soft-shelled turtle, *Lissemys*  
688 *punctata punctata*, and the eastern collard skink, *Chrotaphytus collaris* stain positive for calcium  
689 (Guillette et al., 1989; Sarkar et al., 1995).

690 Viviparous squamates have an absent or reduced eggshell membrane to facilitate gas  
691 exchange (Blackburn, 1993; Braz et al., 2018). Some squamates are encased in the thin  
692 membrane through the entirety of development like the viviparous lizard, *Zootoca vivipara*  
693 (Heulin, 1989). Others have the membrane only in the early stages of embryonic development  
694 like in garter snakes *Thamnophis radix* and *T. sirtalis* (Blackburn & Lorenz, 2003). Calcium  
695 deposits are detected on the outer surface of the membrane throughout development in other  
696 viviparous lizards (Stewart et al., 2013).

697 Reduced number or size of eggshell glands leads to reduced eggshell membrane thickness in  
698 viviparous squamates. In chickens, variation in size, spacing, and neutron density of eggshell  
699 glands may also be important for eggshell structure (Guillette & Jones, 1985). In the  
700 reproductively bimodal Yellow-bellied three toed skink, *Saiphos equalis*, the density of eggshell  
701 glands plays a role in eggshell thickness (Stewart et al., 2010). In the reproductively bimodal  
702 lizard, *Zootoca vivipara*, viviparous individuals have a uterine glandular layer that is less  
703 developed during the stage of eggshell formation compared to oviparous individuals (Heulin et  
704 al., 2005). Additionally, in *Lerista fragilis*, which lays eggs that hatch within just hours of  
705 oviposition, the uterus contains very few mucosal glands (Guillette, 1992). In the fence lizard,  
706 *Sceloporus a. aeneus*, the irregular surface of the eggshell was attributed to the irregular spacing  
707 of shell glands (Guillette & Jones, 1985). In an oviparous gecko, *Hemidactylus turcicus*, their  
708 eggshell glands have loosely packed secretory granules that produce a hard, calcareous shell  
709 (Girling et al., 1998). In a comparison of oviparous and viviparous water snakes from the genus  
710 *Helicops*, viviparous embryos have thinner shell membranes which associated with reduced size  
711 of eggshell glands (Braz et al., 2018). In an oviparous gecko, *Saltuarius wyberba*, their secretory  
712 granules are tightly packed, and their shell is soft and parchmentlike (Girling et al., 1998). In a  
713 viviparous relative, *Hoplodactylus maculatus*, there are far fewer eggshell glands, and where  
714 there are glands, the secretory granules are smaller and more electron dense (Girling, Cree &  
715 Guillette, 1997; Girling, Cree & Guillette, 1998). Smaller eggshell gland size during or after  
716 vitellogenesis is also found in other viviparous squamates compared to oviparous counterparts  
717 (Braz et al., 2018; Gao et al., 2019; Heulin et al., 2005). To my knowledge, in monotremes the  
718 relationship between eggshell thickness and shell gland size, density or compaction of secretory  
719 granules has not been explored.

720 In the oviparous Przewalski's toadhead agama lizard, *Phrynocephalus przewalskii*, 148 genes  
721 are highly expressed in the uterus during the stage of eggshell gland development (Gao et al.,  
722 2019). Only three of these are highly expressed in *P. vlangalii*, a viviparous close relative at this  
723 time, suggesting differences in oviparous and viviparous eggshell gland development requires  
724 regulatory changes to dozens of genes (Gao et al., 2019). In the opossum, a marsupial,  
725 proliferation of uterine glands is not induced by the conceptus (Griffith et al., 2019).

726

### 727 (3) *Evolutionary implications of the physiology of eggshell formation*

728 Presumably because of the influence it has on food production, the process of eggshell  
729 formation has been studied most extensively in chickens (Hincke et al., 2012). The avian  
730 eggshell is formed in a cell-free environment, and it is the fastest calcifying process known to  
731 biology (Hincke et al., 2012; Rodríguez-Navarro et al., 2015). During eggshell formation in  
732 birds, uterine fluid containing a supersaturation of ionized calcium and bicarbonate ions  
733 surrounds the egg (Nys et al., 1991). Transport of calcium in the uterus correlates with plasma  
734 membrane  $\text{Ca}^{2+}$ -ATPase (*PMCA*) activity and with concentrations of calbindin-D28K within  
735 shell gland epithelial cells (Herbert et al., 2006; Wasserman et al., 1991). This leads to the  
736 spontaneous precipitation of calcium carbonate into calcite (Hincke et al., 2012). In the  
737 oviparous lizard, *Lampropholis guichenoti*, immunofluorescence microscopy revealed activity of  
738 *PMCA* in the uterus at the time of eggshell calcification (Thompson et al., 2007).

739 Eggshell formation begins with the eggshell membrane. Two unciliated cell types in the  
740 uterus contribute to eggshell membrane formation in a viviparous skink, *Chalcides ocellatus*  
741 *tiligugu* (Corso et al., 2000). One secretes sulfated glycosaminoglycans to form the inner shell  
742 membrane, and the other which secretes acidic glycoproteins to form the outer layers (Corso et

743 al., 2000). Simple alveolar glands in the lamina propria secrete collagen fibers (Corso et al.,  
744 2000). Inhibition of fiber formation or cross-linking, typically caused by aminopropionitrile or a  
745 copper deficiency, causes distorted formations of the eggshell membrane in birds (Arias et al.,  
746 1997; Chowdhury & Davis, 1995; Hincke et al., 2012).

747 In characteristic Archelosaur eggshells (Choi et al., 2018; Legendre et al., 2022), organic  
748 aggregates are deposited onto the shell membrane creating mammillary knobs, which are absent  
749 in Lepidosaur shells (Choi et al., 2018). Mammillary knobs are a distinct layer between the outer  
750 eggshell membrane and the calcified shell matrix layer (Hamilton, 1986). Part of the mammillary  
751 knobs, called basal caps, are embedded into the outer eggshell membrane fibers (Tyler, 1965).  
752 Mammillary knobs serve as regions of crystal initiation where ACC is deposited (Gautron et al.,  
753 2021) and converted into calcite crystals with no intermediate phase (Rodríguez-Navarro et al.,  
754 2015). Cones are formed that radiate in all upward directions, extending up to the shell matrix  
755 layer (Tyler, 1965). Despite the direct relationship between mammillary knobs and calcium  
756 carbonate crystallization (Rao et al., 2015), the protein comprising mammillary knobs remains  
757 uncharacterized. A keratan sulfate (KS)-proteoglycan, “mammillan”, has been implicated in the  
758 composition of mammillary knobs (Fernandez et al., 2001; Hincke et al., 2012). Any given  
759 proteoglycan is a product of multiple coding genes and biosynthesis of KS-proteoglycans is non-  
760 trivial (Cateron & Melrose, 2018; Funderburgh, 2002; Iozzo et al., 2015). However,  
761 investigations into the keratan sulfate proteoglycan proposed as “mammillan” and identifying its  
762 Properties that Facilitate Calcium Deposition (P-FCD) has far reaching implications given that  
763 KS-proteoglycans are proving to be important players in neurological and cancer research  
764 (Leiphprakpam et al., 2019). The role of homologs of “mammillan” in eggshell formation in  
765 squamates may reveal more about the evolutionary history of the eggshell in amniotes.

766 Parsimony would suggest that all oviparous amniotes shared an ancestral process of  
767 eggshell formation. In Archelosaurs, the process of eggshell formation relies on mammillary  
768 knobs and upward growth of calcite, as described above. In Lepidosaur eggshells, which have  
769 substantially less calcite growth, calcium is deposited on the surface of the eggshell membrane  
770 and, in the case of gekkonids and the tuatara, crystal growth proceeds inward toward the center  
771 (Choi et al., 2018). The strikingly divergent structure and directionality of eggshell formation  
772 between Archelosauria and Lepidosauria suggests that the dissimilar processes of eggshell  
773 formation are a result of genetic drift (e.g. Schiffman & Ralph, 2022), selection for specific  
774 eggshell traits, or, in the case of an early origin of viviparity in Amniotes (Jiang et al., 2023)  
775 and/or Lepidosaurians (Pyron & Burbrink, 2014), eggshells are a derived convergent trait.

776 Hypothetically, if a version of the avian eggshell was the microstructure for basal  
777 Lepidosaurians, loss of mammillary knobs and their basal caps should have prevented calcium  
778 deposition since mammillary knobs are the site at which calcium carbonate spontaneously  
779 precipitates into calcite in Archelosaurs. Given that embryonic signaling supports at least two  
780 main differences between oviparous and viviparous squamates—the timing of calcium secretions  
781 and the length of embryonic retention (Griffith et al., 2015, 2017; Stewart & Eday, 2010)—the  
782 loss of mammillary knobs/basal caps may have supported an early origin of viviparity in  
783 squamates. It would have theoretically facilitated 1) an early loss of the eggshell, 2) enhanced  
784 contact between maternal and embryonic tissues and 3) enhanced signaling from the embryo to  
785 support both altered timing of calcium secretions and hormonal signaling for extended  
786 embryonic retention. This potential mechanism for an early origin of viviparity in squamates is  
787 proposed here, for the first time, as the basal cap hypothesis. When mammillary knobs originated  
788 is of paramount importance to the basal cap hypothesis, and inferences that can be gained from

789 applying it to the evolution of oviparity and viviparity in amniotes. If a version of the avian  
790 eggshell was the ancestral microstructure of oviparous amniotes, the loss of basal caps could  
791 result in a rapid loss of the eggshell and thus a relatively fast transition to viviparity or extended  
792 embryonic retention.

793 Extending to the ancestral state of amniotes (e.g. Jiang et al., 2023; Laurin, 2005; Romero,  
794 1957), absence of functional “mammillan” with P-FCD in squamates and mammals would be  
795 consistent with a derived state of calcified eggshells in Archelosaurs. Absence of functional  
796 “mammillan” with P-FCD exclusively in Lepidosauria would be consistent with the basal cap  
797 hypothesis. Presence of functional “mammillan” with P-FCD across Amniota would be  
798 consistent with the conventional understanding that the amniote egg evolved to prevent  
799 desiccation and enable gas exchange following oviposition of eggs on land (Romero, 1957).  
800 Overall, identifying the evolutionary trajectories of the biosynthetic pathway of “mammillan”  
801 across amniotes is likely to create a better picture of the evolution of the amniote egg.

802 New recommendations for estimating ancestral microstructure of amniote eggshells have  
803 recently been put forth, which abandons the traditional classification of hard/soft/semi-rigid  
804 shells (Legendre et al., 2022). Including the structure of eggshell membranes in viviparous  
805 squamates (e.g. Corso et al., 2000) would also improve phylogenetic reconstructions of the  
806 amniote eggshell.

807 Several pieces of biological evidence lend themselves to an early origin of viviparity in  
808 Lepidosauria and the basal cap hypothesis including—the lack of homology between the semi-  
809 rigid shells of testudines and Lepidosauria (Legendre et al., 2022), the later stage of embryonic  
810 development when eggs are commonly oviposited in squamates (Blackburn, 1995), and the more  
811 predominant reliance on yolk calcium rather than eggshell calcium in squamates compared to

812 Archelosaurs (Packard, 1994; Stewart & Ecaj 2010). Viviparity in the most recent common  
813 ancestor of Lepidosaurians may provide clear evolutionary insights on these phenomena.

814 Other features of eggshells are also worth consideration. In chickens, ovotransferrin is  
815 present in the eggshell membrane and basal cap-layer (Gautron, Hincke, Panhéleux et al., 2001).  
816 Ovotransferrin promotes the development of elongated crystals (Gautron, Hincke, Panhéleux et  
817 al., 2001). The resulting shell matrix is made up of the crystal layer and cuticle (Hamilton, 1986).  
818 On the inner portion of the avian eggshell, it is unclear what prevents growing crystalized cones  
819 from extending into the inner membrane or the albumen. Collagen type X has been implicated  
820 (Arias et al., 1993, 1997; Hincke et al., 2012). The role of collagen type X in creating a boundary  
821 that prevents calcite from passing through the eggshell membrane could inform squamate  
822 eggshells deposition (as discussed, they deposit calcium only on the outer surface, or crystals  
823 grow inward). The only non-avian eggshell matrix protein, pelovaterin, was identified in the soft-  
824 shell turtle (Lakshminarayanan et al., 2005).

825 Over 500 proteins are found in the chicken eggshell matrix (Mann, Maček, & Olsen, 2006;  
826 Mikšík et al., 2007, 2010). Ovocleidin-116 (*OC-116*), ovocalyxin-36 (*OCX-36* or *BPIFB4*),  
827 ovocalyxin-21 (*OCX-21*), and ovocleidin-17 (*OC-17*) are important for avian eggshell formation  
828 (Hernández-Hernández, Gomez-Morales et al., 2008; Jonchère et al., 2010; Tian et al., 2010).  
829 *OC-116*, *OC-36*, *OCX-21*, and *OC-17* are some of the most differentially expressed genes during  
830 eggshell calcification in chickens (Gautron et al., 2007; Hincke et al., 1999, 2012; Jonchère et al.,  
831 2010). Ovocalyxin-21 may serve as a chaperone protein along with the protein endoplasmic  
832 (ENPL) to facilitate proper folding of the avian eggshell matrix (Jonchère et al., 2010). In birds,  
833 *OC-17* is concentrated in the inner mammillary cone layer, it interacts strongly with ACC, and it  
834 is implicated in early stages of biomineralization of the eggshell (Gautron et al., 2021).

835 Originally considered avian-specific, several homologs of avian eggshell matrix proteins  
836 have now been identified in non-avian reptiles and mammals (Le Roy et al., 2021). A recent  
837 study found a significantly reduced number of intact avian eggshell matrix proteins in viviparous  
838 squamates compared to oviparous squamates, a pattern that was especially apparent in snakes  
839 (Xie et al., 2022). This study also found that *OC-17* was only absent in viviparous squamates but  
840 was always present in the oviparous species in the dataset (Xie et al., 2022). Due to this, and the  
841 central role of *OC-17* in avian eggshell formation in birds, they ascribe losing intact *OC17* with  
842 the prevention of reversals back to oviparity (Xie et al., 2022). However, given that *OC-17* is  
843 implicated in initiation of mineralization in the mammillary cone layer, which is absent in  
844 squamates, the necessity of *OC-17* for squamates eggshell formation requires further  
845 investigation. Other genes, like osteopontin (*OPN* or *SPPI*), also play a central role in  
846 biomineralization of the avian eggshell and should be investigated in squamates.

847 *OCX-36* and other bactericidal/permeability-increasing (BPI) family B proteins (also called  
848 *LPLUNCs*) are now thought to have a common origin in vertebrates with multiple duplication  
849 events (Gautron et al., 2007; Tian et al., 2010). Orthologs of *OCX-36* are found in Archelosauria  
850 and Monotremata (Le Roy et al., 2021). In birds, *OCX-36* plays a role in innate immune  
851 responses and is found in high concentrations in the inner eggshell membrane (Gautron et al.,  
852 2007, 2011; Tian et al., 2010).

853 *OC-116* is homologous to mammalian *MEPE*, which plays a role in bone and teeth  
854 mineralization (Bardet et al., 2010a, 2010b). In birds, *OC-116* influences shell thickness, elastic  
855 modulus, and egg shape (Le Roy et al., 2021). *OC-116* was identified in a crocodile, *Crocodylus*  
856 *siamensis*, proteome (Le Roy et al., 2021; Mikšík et al., 2018). Synteny analysis across seven  
857 turtle species and platypus (*Ornithorhynchus anatinus*) revealed absence of *MEPE/OC116* (Le



858 Roy et al., 2021). Other genes and lncRNAs are purported to be important for the quality of  
859 eggshell formation in hens—*FGF14*, *COL25A1*, *GPX8*, and several members of the solute  
860 carrier protein (*SLC*) gene family (Yang et al., 2020). Research into lncRNAs activity in  
861 squamate reproductive tissues during embryonic development represents another valuable track  
862 for research.

863 Various evolutionary genomics studies have revealed squamate-specific candidates for shell  
864 formation (e.g. Recknagel et al., 2021a; Gao et al., 2020). Some of these candidates span the  
865 major clades of amniotes. Seven of the genes expressed during eggshell gland development in  
866 *Phrynocephalus przewalskii*—*HYPOU1*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*, *RRBP1* and  
867 *TRAMI*—are purported to be important for eggshell calcification in chickens (Brionne et al.,  
868 2014). Given this overlap across species that diverged over 300 million years ago (Shen et al.,  
869 2011), these are excellent candidates for further exploration.

870 A functional genomics study harnessed hybridizations of oviparous and viviparous  
871 individuals of *Zootoca vivipara* to reveal 17 SNPs and 38 genes associated with eggshell traits  
872 (Recknagel et al., 2021a). These genes enriched terms related to cell communication and the  
873 immune system, while differentially expressed gene during gravidity enriched pathways for  
874 transforming growth factor (Recknagel et al., 2021a). The three loci with the strongest  
875 association with eggshell traits mapped closely to *LG MN*, *LYPLA1*, and *CRTCI* (Recknagel et  
876 al., 2021a). The association of these genes with eggshell traits is particularly interesting. *LG MN*,  
877 for example, is involved with the cadherin pathway. Cadherins have an established role in  
878 squamate reproduction. In squamates, previous literature discusses how cadherins influence  
879 embryonic attachment in viviparous taxa (Wu et al., 2011). *LG MN* is also differentially  
880 expressed across many viviparous squamates and mammals (Recknagel et al., 2021a). Thus,

881 *LGMN*, appears to support both oviparous and viviparous gestation in different ways. There are a  
882 number of ways to approach exploring how *LGMN* may support both maternal-fetal  
883 interconnectivity (viviparous individuals) and eggshell formation (oviparous individuals). Cell-  
884 to-cell communication analysis using single cell data on uteruses of a reproductively bimodal  
885 species would enable researchers to identify different interaction networks of *LGMN* and  
886 associated cells in oviparous vs viviparous individuals.

887 During gravidity in *Saiphos equalis* two GO terms associated with calcium homeostasis are  
888 enriched by the set of upregulated genes (Foster et al., 2020). However, most of these genes are  
889 associated with regular cellular responses to calcium and even those associated with calcium  
890 transport are upregulated in both early and late stages of gravidity (Foster et al., 2020). Their role  
891 in eggshell formation in this uniquely labile species is therefore ambiguous.

892 In oviparous individuals of another reproductively bimodal skink, *Lerista bougainvillii*, only  
893 two genes are significantly differentially expressed in the gravid uterine tissue compared to non-  
894 gravid uterine tissue (Griffith et al., 2016). No genes are differentially expressed in the gravid  
895 uterine tissue of the oviparous garden skink, *Lampropholis guichenoti*, compared to non-gravid  
896 uterine tissue (Griffith et al., 2016). The genes involved in the shelling process in these species  
897 may not involve changes in expression from the non-gravid state. The dissimilarity in uterine  
898 gene expression profiles across lizards during gravidity suggests there may be multiple ways  
899 oviparous squamates shell their eggs. Given the variation already observed, the eggshell  
900 deposition in squamates should be considered in a phylogenetic context and under the different  
901 evolutionary history inferred by ancestral state reconstructions (Harrington & Reeder, 2017;  
902 Pyron & Burbrink, 2014). Supplementary table 1 compares candidate genes associated with  
903 eggshell formation and shell gland development in squamates to that of birds.

904

905 (4) *Pleiotropy of genes and proteins involved with eggshell formation*

906 Substantial pleiotropy of genes involved with eggshell formation would imply that regardless  
907 of parity mode, taxa have innately conserved toolkits that can be readily exploited to form an  
908 eggshell for oviparous gestation. In addition to the candidate genes associated with both  
909 gestation length and eggshell traits in *Zootoca vivipara* (Reckagel et al., 2021a), several genes  
910 associated with eggshell deposition have pleiotropic effects within species or have different  
911 effects in oviparous vs. viviparous amniotes. Osteopontin (*SPP1* or *OPN*) is found in bone and  
912 kidneys, and transports calcium to other tissues in the body (Pines et al., 1995). It plays an  
913 important role in calcium carbonate biomineralization of the avian eggshell (Gautron et al.,  
914 2021). It is highly expressed in the chicken uterus during calcification (Jonchère et al., 2010) but  
915 supports pregnancy recognition and implantation in sheep (Bazer et al., 2011). Improper  
916 functioning of *SPP1* in the uterus leads to cracked and abnormal shells in birds (Arazi et al.,  
917 2009; Hincke et al., 2008).

918 When expressed in the uterus, some bone morphogenic protein-coding genes (*BMPs*) aid  
919 eggshell calcification (Jonchère et al., 2010). *BMPs* are part of the *TGF- $\beta$*  superfamily and are  
920 involved with the formation of new cartilage and bone, and with biomineralization in corals and  
921 mollusks (Canalis et al., 2003; Lelong et al., 2000; Zoccola et al., 2009). Chordin (*CHRD*) is an  
922 antagonist of the *BMP* pathway. *BMP*-binding endothelial regulatory protein (*BMPER*) and  
923 *CHRD* are expressed in the chicken uterus during the stage of eggshell calcification (Jonchère et  
924 al. 2010). Regulation of *BMPs* by *CHRD* is essential for early embryogenesis and adult  
925 homoeostasis.

926 *BMPER* and seven *BMPs* are expressed during gestation in *Chalcides ocellatus*, a viviparous  
927 skink (Brandley et al., 2012). Most of these are upregulated (Brandley et al. 2012). *BMP* genes  
928 are expressed during both gravidity and non-gravidity in oviparous *Lerista bougainvillii* and  
929 *Lampropholis guichenoti* (Griffith et al., 2016). *BMP2* is upregulated in oviparous late gestation  
930 compared to viviparous late gestation in the reproductively bimodal lizard, *Saiphos equalis*  
931 (Foster et al., 2020).

932 Differential expression of *BMPR1B* is associated with differences in eggshell quality in  
933 chickens (Yang et al., 2020). Another study associated stage-specific high-expression of  
934 *BMPR1B* with the stage corresponding to extended embryonic retention and placentation in  
935 *Phrynocephalus vlangalii* (Gao et al., 2019). They identified a co-expression network of highly  
936 expressed genes, including *BMPR1B*, that they associated with placentation (Gao et al., 2019).  
937 *BMPR1B* also reaches significant levels of differential expression in uterine tissues of other  
938 gestating viviparous lizards, *Chalcides ocellatus* and *Pseudemoia entrecasteauxii*, compared to  
939 non-gestational uterine tissue (Brandley et al., 2012; Griffith et al., 2016). Receptors for *BMPs*  
940 are also expressed in the uterus during gestation in other viviparous lizards, *Phrynocephalus*  
941 *vlangalii* and *Pseudemoia entrecasteauxii* (Gao et al., 2019; Griffith et al., 2016). Perhaps  
942 unsurprisingly, *BMPR1B* is also differentially expressed in the uterus of viviparous *Zootoca*  
943 *vivipara* compared to oviparous individuals during gestation.

944 The potential role of these genes in squamate eggshell formation remains unclear. *BMPs*  
945 influence on dorsal-ventral axis patterning during early embryogenesis and growth of skeletal  
946 structures in post-natal tissues (Medeiros & Crump, 2012). It may be difficult to disentangle their  
947 roles in embryonic development, placental development, and eggshell deposition. Future  
948 research on them may inform scientific understanding of parity mode evolution.

949 *SLIT* genes are purported to be involved with folding the eggshell matrix in chickens  
950 (Jonchère et al., 2010). The *SLIT2* gene functions across birds and mammals in diverse organs,  
951 and encodes a protein that provides a structural framework for protein-protein interactions  
952 (Jonchère et al., 2010; Marillat et al., 2002). In a functional genomics study, *SLIT2* was  
953 identified as an important gene for eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).  
954 *SLIT2* is among the 50 most downregulated genes in the uterus during pregnancy in the  
955 viviparous African ocellated skink, *Chalcides ocellatus*, compared to non-pregnancy (Brandley  
956 et al., 2012). However, in the uterus of the yolk-sac placenta in the viviparous skink, *Pseudemoia*  
957 *entrecasteauxii*, *SLIT2* is upregulated compared to non-reproductive uterine tissue (Griffith et al.,  
958 2016). *SLIT3* is differentially expressed during the stage of placentation in the viviparous agama  
959 lizard, *Phrynocephalus vlangalii* (Gao et al., 2019). *SLIT* genes also play a role in axonal  
960 pathfinding and neuronal migration in rats (Marillat et al., 2002). *SLIT2* was associated with  
961 reproduction in humans (Chen, Chu et al., 2015).

962 Podocalyxin (*PODXL*) is a sialoprotein associated with eggshell calcification in chickens  
963 (Jonchère et al., 2010). In the viviparous Qinghai toad-headed agama lizard, *Phrynocephalus*  
964 *vlangalii*, a weighted gene correlation network analysis associated *PODXL* with uterine  
965 structural changes (Gao et al., 2019). The gene may play a role in placentation in these species  
966 given that it was also differentially expressed in the uterus during the stage of placentation (Gao  
967 et al., 2019). Interestingly, *PODXL* is downregulated in the uterus of the yolk-sac placenta in  
968 another viviparous skink, *Pseudemoia entrecasteauxii* (Griffith et al., 2016). Based on its role in  
969 chickens and *P. vlangalii*, *PODXL* is a good candidate for further research on the molecular  
970 evolution of eggshell formation and placentation in squamates.

971

972 (5) *Eggshell formation termination*

973 When eggshell formation is terminated, the egg is still bathed in the supersaturated  
974 calcium and bicarbonate ion fluid (Hincke et al., 2012). Some component(s) of the terminal  
975 uterine fluid may prevent precipitation of calcium carbonate (Gautron, Hincke & Nys, 1997),  
976 such as phosphate anions (Lin & Singer, 2005). The presence of phosphorous in the superficial  
977 layers of the chicken shell suggest it may be a factor preventing the deposition of calcite crystals  
978 in the terminal stage. Additionally, the high concentration of *OCX-32* in the outer eggshell and  
979 cuticle, suggest that the gene may inhibit proteinaceous crystal growth in the terminal stage of  
980 eggshell calcification (Gautron, Hincke, Mann et al., 2001). It is informative to viviparous  
981 reproduction and consistent with the basal cap hypothesis that exposure to precursors of the  
982 eggshell does not necessitate eggshell deposition. The influence of phosphate anions and *OCX-*  
983 *32* on inhibition of calcium carbonate precipitation on the eggshell membrane of viviparous  
984 squamate embryos has not been examined to my knowledge.

985

986 (6) *Rotating the egg for eggshell formation*

987 Oviparous amniotes rotate the egg for calcium formation and viviparous mammals rotate the  
988 embryos for parturition. One hurdle to reversing back to oviparity may be re-evolving rotation of  
989 the egg for shell formation early in gravidity (Griffith et al., 2015). Given the complex  
990 musculature of the uterus across taxa, that allows for multidirectional force for parturition and  
991 eggshell formation, it is difficult to determine the degree of difficulty for re-evolving appropriate  
992 timing of egg-rotation. Cadherins and hormonal signaling support embryonic attachment (Wu et  
993 al., 2011; Biazik et al., 2012), which can prevent rotation of the egg. Oviparous taxa lack  
994 embryonic attachment, enabling the uterus to rotate the egg for eggshell formation. This rotation

995 does not happen until later in gestation for eutherian mammals when, for example, the embryo  
996 detaches and cadherins become less concentrated (Wu et al., 2011). Perhaps a candidate gene for  
997 studying this is, a cadherin *CDH5*, the only gene that is differentially expressed in all viviparous  
998 squamates studied thus far studied (Recknagel et al., 2021a). Genes that enrich the GO term for  
999 “voltage-gated calcium channel activity” are also useful candidates for investigating uterine  
1000 rotation associated with eggshell formation because voltage-gated calcium channels effect the  
1001 action potential of cells and can cause muscle contractions.

1002

### 1003 (7) Discussion & future directions—eggshell formation and parity mode evolution

1004 The process of eggshell formation is more resolved in birds compared to non-avian reptiles  
1005 and monotremes (Choi et al., 2018; Frankenberg & Renfree 2018). I described some overlaps  
1006 gleaned from the literature which prove as curious candidates for further research  
1007 (Supplementary Table 1). Of particular interest are avian eggshell matrix proteins (Alföldi et al.,  
1008 2011; Le Roy et al., 2021; Tian et al., 2010; Xie et al., 2022), genes with biomineralizations  
1009 functions, candidate genes associated with eggshell traits in *Zootoca vivipara* (Recknagel et al.,  
1010 2021a), and the homologs for avian eggshell matrix proteins identified in the *Anolis carolinensis*  
1011 genome (Alföldi et al., 2011; Tian et al., 2010). Additionally, genes purported to be important for  
1012 eggshell calcification in chickens associated with eggshell gland formation in an oviparous  
1013 lizard, *Phrynocephalus przewalskii*, are relevant—*HYPOUI*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*,  
1014 *RRBP1* and *TRAMI* (Brionne et al., 2014; Gao et al., 2019). Overlaps between the genes  
1015 associated with gestation length and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a)  
1016 hint at genes that could potentially evolve to innately effect multiple traits relevant to parity  
1017 mode transitions. The basal cap hypothesis also offers a simple evolutionary mechanism to

1018 investigate the evolutionary history of amniote parity mode evolution (see section III.3).  
1019 Alternatives to the basal cap hypothesis are that dissimilar eggshells and eggshell deposition  
1020 processes evolved through selective pressure, genetic drift, or both. Fortunately, the basal cap  
1021 hypothesis can be utilized to ascertain the likelihood of this.

1022

#### 1023 **IV. Placentation & Transport of Embryonic Water, Gas, and Nutrients**

1024

1025 The evolutionary pressures on fluid allocation, gas exchange and nutrient transport should  
1026 differ between oviparous and viviparous taxa because their sources of all or some of these  
1027 resources differ (Blackburn, 1992; Bonnet et al., 2001; Bonnet, Naulleau & Shine, 2017; van  
1028 Dyke et al., 2014). In viviparity, maternal gas and water are accessed through the chorioallantois,  
1029 which is especially important in the latter half of development (van Dyke et al., 2014; Carter,  
1030 2012). Nutrients can be available from the yolk, maternal transfer, or both yolk and maternal  
1031 transfer.

1032 While viviparity is associated with shared patterns of uterine gene expression during amniote  
1033 gestation (Recknagel et al., 2021a), the same does not occur in viviparous amniote placentas  
1034 (Foster et al., 2022). Instead, different genes that serve similar functions are recruited to the  
1035 placenta across independent origins of viviparity (Foster et al., 2022). Additionally, where other  
1036 amniotes can rely on the albumen for fluid allocation, squamates lack an albumen (Blackburn &  
1037 Stewart, 2021). The eggshells of various squamates supports uptake of water from the  
1038 environment (Blackburn & Stewart, 2021). The evolutionary implications of this have not been  
1039 documented to my knowledge.

1040



1041        *(1) Anatomy & methods of water, gas & nutrient provisioning*

1042        The embryonic membranes regulate embryonic fluid transport, nutrient supply, respiration,  
1043 immunity, and waste (Brace, 1997; Burton & Tullett, 1985; Ferner & Mess, 2011; Packard &  
1044 Packard, 1980). Fluids are important for the developing embryo because they prevent desiccation  
1045 and compression (Ferner & Mess, 2011; Packard & Packard, 1980). Over-abundance or under  
1046 abundance of embryonic sac fluids leads to reproductive failure (Chamberlain et al., 1984;  
1047 Fedakâr et al., 2016; Hadi, Hodson & Strickland, 1994; Mercer et al., 1984). Water is the  
1048 predominant resource provisioned from the mother in most viviparous squamates (Lourdais et  
1049 al., 2015).

1050        Oxygen flux in embryonic mammals is largely determined by oxygen-diffusing capacity of  
1051 the placenta, the rates of blood flow in the umbilical and uterine arteries, and the oxygen  
1052 capacities and affinities of fetal and maternal blood (Carter, 2009). Reptilian and mammalian  
1053 blood vessels differ in basic characteristics such as capillary density, capillary surface, and  
1054 oxygen diffusion gradients (Pough, 1980). Oviparous taxa regulate gas exchange through pores  
1055 in their eggshells.

1056        Patterns of embryonic nutrient exchange can be broadly categorized into lecithotrophy,  
1057 obtaining nutrients from the yolk, and placentrophy or matrotrophy, obtaining nutrients from the  
1058 mother. Taxa belonging to Archelosauridae are lecithotrophic. The ancestral state of mammals  
1059 was most likely oviparous matrotrophy that later evolved into viviparous matrotrophy in therians  
1060 (Blackburn, 2005). The ancestral state of reptiles was likely lecithotrophy (Blackburn, 2005).  
1061 Most viviparous squamates are lecithotrophic, some are lecithotrophic and matrotrophic, and a  
1062 few have specializations for substantial matrotrophy (e.g. Blackburn, 2015a, Blackburn, 1985b;  
1063 Stewart & Thompson, 1993; Thompson, Stewart et al., 1999; van Dyke et al., 2014). Even in

1064 lecithotrophic viviparous squamates some degree of organic or inorganic nutrients pass through  
1065 the chorioallantoic placenta (Blackburn, 2005; Swain & Jones, 1997, 2000; Stewart & Eca, 2010; Thompson, Stewart et al., 1999; Thompson & Speake, 2002). Reversals may be most  
1066 unlikely in lineages that have specialized placentas for substantial nutrient exchange because  
1067 they would need to re-evolve lecithotrophy. Highly matrotrophic squamates are extremely rare  
1068 (Blackburn, 2015a).

1070

1071 *(2) Evolutionary history of yolk-sac formation and yolk processing*

1072 Vitellogenesis is the process of yolk formation in the oocyte, providing the embryo with a  
1073 valuable source of nutrients, primarily through the accumulation of precursor proteins to yolk,  
1074 vitellogenins. Vitellogenin is produced in the liver, called hepatic vitellogenesis, and transported  
1075 to the maturing ovum (Ho, 1987). Vitellogenins were lost in all mammals except monotremes  
1076 (Brawand, Wahli & Kaessmann, 2008). They are a primary source of nutrition for other  
1077 amniotes. Functionally similar to vitellogenin, caseins have persisted in all mammalian milks  
1078 (Brawand et al., 2008). Active functioning of the yolk sac is restricted to the first trimester in  
1079 placental mammals, and it is postulated to provide nutrients to the embryo (Kuzima et al., 2023).  
1080 The detection of glycodelin in the yolk sac epithelium also supports this (Burton et al., 2002). In  
1081 the yolk-sac of bats, dogs, and non-human primates the mesoderm derived layer is absorptive  
1082 and may transfer substances from the exocoelomic cavity where the yolk sac is located (Enders  
1083 et al., 1976; Freyer & Renfree, 2009; King & Wilson, 1983; Lee et al., 1983).

1084 The morphology of the yolk-sac and process of vitellogenesis differs between birds and non-  
1085 avian reptiles. In birds, during the process of meroblastic cleavage, the zygote's cells divide  
1086 while the yolk component does not. The yolk forms a large, fluid, non-cellularized mass

1087 surrounded by the extraembryonic yolk sac. The formation of the yolk-sac placenta in birds has  
1088 the following pattern—first the bilaminar omphalopleure forms and then trilaminar  
1089 omphalopleure; blood vessels move into folds of the extraembryonic endoderm, becoming  
1090 stratified epithelium; the folds carrying the blood vessels reach the peripheral regions of the yolk  
1091 only and the center of the yolk mass remains uncellularized (Starck, 2021). Intensive  
1092 development of hemopoietic tissue surrounding the blood vessels during most of embryonic  
1093 development, thus far, appears to be unique to birds (Starck, 2021). Compared to non-avian  
1094 sauropsids, the unique pattern of yolk processing in birds facilitates faster embryonic  
1095 development (Blackburn, 2021).

1096 The yolk sac characteristic of non-avian reptilian eggs serves as a model for the transition  
1097 between the egg of anamniotes and amniotes (Blackburn, 2020). A series of recent papers,  
1098 covering species of snakes, lizards, crocodiles, and turtles, indicate that these taxa utilize similar  
1099 developmental pathways of yolk-sac formation and yolk processing that differs from birds  
1100 (Blackburn, 2020, 2021; Blackburn et al., 2019; Elinson et al., 2014; Elinson & Stewart 2014;  
1101 Stinnett et al., 2011). Across these taxa, a bilaminar/trilaminar omphalopleure overgrows the  
1102 yolk mass, and the yolk mass gets invaded by proliferating endodermal cells that phagocytose  
1103 the yolk material. These cells form clumps, progressively filling the yolk mass. Small blood  
1104 vessels derived from yolk sac vasculature invade the yolk sac cavity and the endodermal cells  
1105 arrange in monolayers around these vessels, forming “spaghetti bands” (Blackburn, 2021). The  
1106 yolk sac of *Pantherophis guttatus* is one suitable model for studying the transition of the yolk-  
1107 sac from anamniotes to amniotes (Elinson & Stewart, 2014; Elinson et al., 2014).

1108 A major difference between non-avian reptilian yolk-sac formation is the morphology and  
1109 extent of vascularization and cellularization in the yolk sac cavity (Starck, 2021). Birds have a

1110 yolk-sac with absorptive endodermal lining that digests nutrients and send them into blood  
1111 circulation (Starck, 2021) whereas snakes, lizards, turtles, and crocodilians have a yolk sac that  
1112 becomes invaded by endodermal cells that proliferate and phagocytose yolk material (Blackburn,  
1113 2021). In these taxa, yolk material becomes cellularized, digested, and transported by vitelline  
1114 vessels to the developing embryo (Blackburn, 2021). Factors involved with cellularization of the  
1115 yolk-sac are proposed to include cell cycle regulators and structural proteins (Elinson et al.,  
1116 2014). Generation of these cells are suspected to be reliant on processes of angiogenesis and are  
1117 likely transcriptionally active (Elinson et al., 2014). Few transcriptomic profiles of yolk-sac  
1118 placentas in reptiles have been documented to my knowledge (Griffith et al., 2016). Significant  
1119 overlaps in the yolk-sac transcriptomes of human, mice, and chicken—including apolipoproteins  
1120 and SLC transporters—however, suggest functional conservation (Cindrova-Davies et al., 2017).

1121 As discussed in a previous section, progesterone inhibits myometrial contractility, but it also  
1122 inhibits estrogen-induced hepatic vitellogenin synthesis (Custodia-Lora, Novillo, & Callard,  
1123 2004; Callard et al., 1992). Variable progesterone concentrations in circulation throughout  
1124 gestation in viviparous squamates may reflect a trade-off to allow estrogen expression to support  
1125 hepatic vitellogenin synthesis during embryonic development, thus supporting nutrient  
1126 provisioning during the lengthened embryonic retention. Although hepatic vitellogenesis usually  
1127 ceases during gestation, vitellogenin synthesis and mother-to-embryo transfer was detected in  
1128 one viviparous fish, *Xenotoca eiseni*, during gestation (Iida et al., 2019). Future research should  
1129 consider the timing of vitellogenin synthesis throughout the reproductive cycle in gestating and  
1130 non-gestating viviparous squamates to investigate this further.

1131

1132 (3) *Evolutionary history of placentrophy in mammals & squamates*

1133 Traditionally, it was thought that placentrophy evolved after viviparity in squamates  
1134 (Packard, Tracy, & Roth, 1977; Shine & Bull, 1979). Further research demonstrated that  
1135 placentrophy and viviparity evolved simultaneously (incipient matrotrophy) in mammals and  
1136 may have in squamates (Blackburn, 1985, 1992, 2005, 2006; Stewart & Eday, 2010). The  
1137 incipient matrotrophy model relies on evidence that 1) uterine provisioning of nutrients predates  
1138 the origin of viviparity (Blackburn 1985, 1992, 2006), 2) uterine and embryonic tissues have a  
1139 close anatomical and physiological association in viviparous taxa and 3) some degree of  
1140 placental transfer of organic or inorganic molecules occurs in viviparous taxa (Stewart & Eday,  
1141 2010). In squamates, the potential for both incipient matrotrophy and evolution of placentrophy  
1142 after viviparity is supported (Stewart & Eday, 2010). Facultative placental nutrient provisioning  
1143 and incipient matrotrophy may have driven the evolution of squamates with substantial  
1144 matrotrophic nutrient provisioning (Stewart, 2020; Swain & Jones, 2000).

1145 Placentation and implantation are not homologous in mammals compared to squamates  
1146 (Griffith, van Dyke & Thompson, 2013). Several placental specializations for gas and nutrient  
1147 exchange are unique to mammals including erosion of the uterine mucosa, extensively invasive  
1148 implantation, hemochorial contact, retention of a vascularized choriovitelline membrane, and  
1149 countercurrent patterns of blood flow (Blackburn, 2005). This enables extensive exchange of  
1150 nutrients in addition to water and gas. The vast majority of viviparous squamates have the most  
1151 superficial type of chorioallantoic placenta called epitheliochorial placenta (Blackburn, 1993).

1152 Nutrient provisioning through placentrophy is obligate for embryonic development in only  
1153 five lineages of squamates, all of which are scincid lizards (Blackburn, 2000; Flemming &  
1154 Blackburn, 2003; Ramírez-Pinilla et al., 2011; van Dyke et al., 2014). *Pseudemoia*  
1155 *pagenstecheri*, a lizard with a highly specialized placenta, out-performs lecithotrophic oviparous

1156 close relatives in the relative amount of nutrients it transfers to the embryo (Stewart et al., 2009).  
1157 *Pseudemoia entrecasteauxii* is a moderately matrotrophic viviparous skink, with roughly half of  
1158 embryonic nutrient uptake from the yolk and half through a specialized cyto-epitheliochorial  
1159 placenta (Adams et al., 2005; Speake et al., 2004; Stewart & Thompson, 1993, 2009).

1160 Specializations of the chorioallantoic placenta for nutrient provisioning in some squamates  
1161 include elaborate specializations for uterine secretion and absorption, including placentomes,  
1162 chorionic areolae, hypertrophied uterine mucosa, and chorionic epithelia modified for absorption  
1163 (Blackburn, 2005). In squamates, specializations for gas exchange across the chorioallantoic  
1164 placenta include decreased diffusion distance between maternal and fetal capillaries, uterine  
1165 vascularity, shell membrane deterioration, and modifications of both fetal and maternal blood  
1166 properties (Blackburn, 1998, 2005; Blackburn & Lorenz, 2003; Blackburn & Vitt, 2002).

1167 Mammalian placenta-specific genes have deep origins in vertebrates (Rawn & Cross, 2008).  
1168 Placentation to support viviparity likely employs genes that are ancestral to the chorioallantois.  
1169 However, one study that looked at placentation and gene expression across a small sample of  
1170 divergent amniotes found only one gene with a placentrophy-specific pattern of gene expression,  
1171 *DIO3* (Griffith, Brandley et al., 2017). In mammals, *DIO3* is an imprinted gene and  
1172 preferentially paternally expressed. The authors suggest that the gene may increase offspring  
1173 resource uptake during pregnancy in the horse and a viviparous lizard, *Pseudemoia*  
1174 *entrecasteauxii*, where it is recruited to the placenta (Griffith, Brandley et al., 2017).

1175

#### 1176 (4) *Genes involved with embryonic water, gas, and nutrient transport*

1177 Water transport in animals is regulated by a family of molecular water channels called  
1178 aquaporins (AQs or AQPs) (Borgnia et al., 1999). In humans, *AQP1*, *AQP3*, *AQP4*, *AQP8* and

1179 *AQP9* are found in the placenta but further research is needed to understand how these influence  
1180 water fluxes between maternal and fetal tissues (Damiano, 2011). Transcriptomic analysis on  
1181 uterine tissue of the gestating, viviparous skink, *Chalcides ocellatus*, reveal differential  
1182 expression of *AQP1*, *AQP3*, *AQP5*, *AQP6*, *AQP8*, *AQP9* and *AQP11* when compared to non-  
1183 gestating uteruses (Brandley et al., 2012). In birds, *AQP1* is expressed in the chorioallantoic  
1184 membrane, and it is suggested to influence angiogenesis throughout embryonic development  
1185 (Ribatti et al., 2002). In a viviparous lizard, *Pseudemoia entrecasteauxii*, *AQP8* and *AQP9* were  
1186 more highly expressed in the chorioallantoic placenta compared to the yolk-sac placenta (Griffith  
1187 et al., 2016). During gestation in both oviparous and viviparous populations of the reproductively  
1188 bimodal skink, *Saiphos equalis*, several genes involved with water homeostasis are upregulated  
1189 in the uterus including *AQP1*, *AQP3* and *AQP12B* (Foster et al., 2020). In uteruses of *Saiphos*  
1190 *equalis*, *AQP5* and *AQP8* are upregulated during oviparous late gestation compared to viviparous  
1191 late gestation. In sheep, *AQP3* is differentially expressed during gestation, where it serves a dual  
1192 role of water transport to the embryo and fetal urea export (Johnston et al., 2000). This is similar  
1193 to the function of *AQP9* in humans (Damiano, 2011). Immunocytochemistry reveals that *AQP1*  
1194 and *AQP3* are expressed in the uterus of the highly placentrophilic South American scincid lizard,  
1195 *Mabuya sp.* (Wooding et al., 2010). In *Zootoca vivipara*, *AQP9* is upregulated at midgestation  
1196 (Recknagel et al., 2021a).

1197       Some molecules are implicated in the regulation of aquaporins including insulin (INS),  
1198 human chorionic gonadotropin (HcG), cyclic adenosine monophosphate (cAMP) and cystic  
1199 fibrosis transmembrane conductance regulator (CFTR) (Damiano, 2011). Genes predicted to be  
1200 involved with reproduction in *Anolis carolinensis* are enriched for the GO term for cAMP-  
1201 mediated signaling (Alföldi, Di Palma, et al., 2011). Further comparative research should be

1202 done to elucidate the functional differences of aquaporins in oviparous and viviparous amniotes  
1203 and how they relate to the differing conditions under which these embryos develop.

1204 Genes involved embryonic oxygen transport precede the origin of amniotes. Hemoproteins  
1205 arose in evolutionary history well before they were used for placental oxygen transfer (Hardison  
1206 1998). In mammals, adult (Alpha: HBA; Beta: HBB, HBD) and embryonic hemoglobins (Alpha:  
1207 HBZ, HBA; Beta: HBE, HBG, and HBH) are involved with oxygen transport (Carter, 2012).  
1208 Some of these are unique to eutherian mammals following a series of duplication events (Opazo  
1209 et al., 2008). However, fetal hemoglobins are found in turtles, lizards, and snakes (Pough, 1980).  
1210 HBA, HBB and HBM are all significantly downregulated in the uterine tissue of the viviparous  
1211 African Ocellated Skink, *Chalcides ocellatus*, during gestation compared to non-gestation  
1212 (Brandley et al., 2012). The oxygen demands of reptile embryos are relatively low until stage 30,  
1213 when most oviparous taxa oviposit (Shine & Thompson, 2006). In viviparous and oviparous  
1214 species with long egg retention, embryonic demand for maternal provision of oxygen and  
1215 removal of CO<sub>2</sub> increases at this stage.

1216 Improper water, gas and nutrient exchange can occur due to poor chorioallantoic blood flow  
1217 (Wootton et al., 1977). Thus, viviparous taxa require greater degrees of vascularization and  
1218 vasodilation to facilitate enhanced requirements for maternal resources compared to oviparous  
1219 taxa. Rather than increasing the size of the placenta, increasingly dense blood vessels can support  
1220 fetal growth without compromising space for embryonic growth as occurs in some pigs (Ford,  
1221 1997; Vonnahme et al., 2002). Embryonic vascularization and vasodilation are dependent on  
1222 signals from the endoderm (Jin et al., 2005; Vokes & Krieg, 2002; Wilt, 1965). In oviparous  
1223 individuals of *Saiphos equalis*, populations with extended egg retention, there is expansion of the  
1224 uterine vascular bed and thickening of the chorioallantoic tissue that supports increased



1225 embryonic growth in the later portion of oviparous gravidity (Parker et al., 2010). In the  
1226 viviparous scincid lizard, *Eulamprus quoyii*, angiogenesis, the formation of new blood vessels,  
1227 and expansion of the vessel-dense elliptical area of the uterus is associated with supporting  
1228 increased embryonic oxygen demand (Murphy et al., 2010).

1229       Several protein-coding genes are known to be involved with angiogenesis, vascularization,  
1230 and vasodilation in utero. One study that examined expression patterns across chickens  
1231 (oviparous), horses (viviparous), two viviparous squamates, and one oviparous squamate found  
1232 that no examined genes for angiogenesis showed a viviparity-specific expression pattern  
1233 (Griffith, Brandley et al., 2017). However, other than the chicken, the only oviparous taxa  
1234 included in this study was a reproductively bimodal skink, *Lerista bougainvillii* (Griffith,  
1235 Brandley et al., 2017). Alternatively, differential gene expression analyses on oviparous and  
1236 viviparous individuals of *Zootoca vivipara*, revealed pathways for angiogenesis enriched in  
1237 viviparous female reproductive tissues; and pathways for angiogenesis were enriched across  
1238 genes under divergent selection in oviparous and viviparous *Z. vivipara* individuals.

1239       In the uterine tissue of gestating viviparous skinks and rats, several genes for angiogenesis  
1240 are upregulated—*EPASI*, *HIF1A* and *VEGFA* (Brandley et al., 2012; Whittington et al., 2015,  
1241 2017). Other proteins involved in vascularization and vasodilation in utero include members of  
1242 the vascular endothelial growth factor (*VEGF*) gene family, VEGF receptors (*VEGFRs*),  
1243 placental growth factor (*PGF*) and nitric oxide synthase (*NOS*) (Blomberg et al., 2010; Chen,  
1244 Wang et al., 2015; Gilbert, 2010; Reynolds et al., 2006; Risau, 1997; Torry et al., 2003;  
1245 Vonnahme et al., 2001). In *Saiphos equalis*, different homologs of *NOS* experience different  
1246 patterns of gene expression across the oviparous and viviparous stages of gestation/gravidity  
1247 (Foster et al., 2020). One homolog of *NOS* is upregulated during oviparous late gestation, and

1248 another is upregulated during viviparous late gestation (Foster et al., 2020). Several genes  
1249 involved with angiogenesis and vascular morphogenesis are downregulated in the pre-  
1250 implantation uterus of a marsupial, the Fat Tailed Dunnart, *Sminthopsis crassicaudata*—  
1251 *ADGRA2*, *ADGRB2*, *ANGPTL1*, *EPHB4*, *ISM1*, *PDZRN3*, *RHOJ*, *TNMD*, and *VEGFD*  
1252 (Whittington et al., 2018).

1253 In humans, immune factors are also responsible for increasing embryonic blood supply.  
1254 Embryonic non-classical MHC class I molecule, HLA-G, and uterine natural killer (uNK) cells  
1255 support increased embryonic blood supply (Moffett & Loke, 2006; Rajagopalan et al., 2006). A  
1256 similar pattern of utilizing immune properties to support embryonic blood supply has not been  
1257 yet identified in squamates.

1258 Lipids are a main energy source for embryos. Lipoprotein lipase (LPL) is an important  
1259 enzyme in lipid transport. LPL is significantly expressed on the syncytiotrophoblasts, specialized  
1260 placental cells, of humans (Lindegaard et al., 2005) and the endometrium of cows (Forde et al.,  
1261 2011), and pigs (Ramsay et al., 1991), where it plays a role in lipid mobilization. A viviparous  
1262 lizard, *Pseudemoia entrecasteauxii*, increases capacity for lipid transport toward the end of  
1263 pregnancy (Griffith, van Dyke & Thompson, 2013). The uterine tissue of the yolk-sac placenta in  
1264 this species had significantly higher expression of LPL than the uterine tissues of the  
1265 chorioallantoic placenta (Griffith, van Dyke & Thompson, 2013), leading the authors to suggest  
1266 that the yolk-sac placenta is the major site of lipid transport. LPL expression was not detected  
1267 during pregnancy in the viviparous skink, *Chalcides ocellatus* (Blackburn, 1992; Brandley et al.,  
1268 2012). Instead, lipid transport may be facilitated by fatty acid binding proteins in this species  
1269 (Chmurzyńska, 2006; Brandley et al., 2012). These are also active on mammalian placenta  
1270 (Haggarty, 2002).

1271 Apolipoproteins are also suitable candidates for transport of fatty acids, cholesterol, and  
1272 phospholipids. Five of these (*APOA1*, *APOA2*, *APOA4*, *APOE*, and *APOM*) and *APOA1BP* are  
1273 significantly upregulated in the pregnant uterus of the viviparous skink, *Chalcides ocellatus*  
1274 (Brandley et al., 2012). *APOA1BP* is also upregulated in the uterus of the chorioallantoic  
1275 placenta and yolk-sac placenta compared to non-gestational uterine tissues in *Pseudemoia*  
1276 *entrecaeauxii* (Griffith et al., 2016). Additionally, upregulation of 136 genes that encode solute  
1277 carrier proteins (SLCs) in the pregnant uterus of *Chalcides ocellatus* are associated with  
1278 transport of inorganic ions, metals, glucose, amino acids, peptides, fatty acids, and carboxylic  
1279 acids (Brandley et al., 2012).

1280 Supply of amino acids is required for embryonic development. SLCs have important  
1281 transport functions, including the transport of amino acids, and thus they are considered to be  
1282 important for gestation (Foster et al., 2022). However, a recent study found no overlap in the  
1283 amino acid transporting SLCs upregulated in placentas of viviparous placentrophic vertebrates  
1284 studied, which included eight representatives from Mammalia, Reptilia, and Chondrichthyes  
1285 (Foster et al., 2022). However, *SLC38A3* was upregulated in all viviparous species except *Rattus*  
1286 *norvegicus* (Foster et al., 2022).

1287 Cathepsins and phospholipases are important for uterine secretions for embryonic  
1288 development in horses, pigs, sheep, and cattle (Bazer, 1975; Satterfield et al., 2007; Song et al.,  
1289 2010). Cathepsins are present in yolk sacs of humans and mice. They function to degrade  
1290 proteins to free amino acids (Cindrova-Davies et al., 2017). Two genes for cathepsin L (*CTSL1*  
1291 and *CTSL2*) are upregulated in the uterus during gestation in *Chalcides ocellatus* (Brandley et al.,  
1292 2012). *CTSL* is also upregulated in the uterus during the pre-implantation phase in the Fat-Tailed  
1293 Dunnart, *Sminthopsis crassicaudata* (Whittington et al., 2018), and in the uterus of the

1294 chorioallantoic placenta and uterus of the yolk sac placenta during gestation in *Pseudemoia*  
1295 *entrecasteauxii* (Griffith et al., 2016).

1296 In viviparous individuals of the reproductively bimodal lizard, *Saiphos equalis*, many genes  
1297 for cellular adhesion are upregulated during late gestation (Foster et al., 2020). The authors  
1298 postulated that this helps facilitate maternal-fetal signaling and paracellular transport (Foster et  
1299 al., 2020). Gao et al. (2019) identified a set of genes in *Phrynocephalus vlangalii* that were  
1300 differentially expressed in the uterus during the stage of placentation and these enriched GO  
1301 terms functionally related to the process of placentation. This included an estrogen receptor  
1302 (*ESRI*) and two growth factor receptors (*GHR* and *IGFIR*) (Gao et al., 2019).

1303 Finally, the proteomes of the ovary and placenta from obligately placentrophic *Mabuya*  
1304 lizards can further serve as a useful resource for examining nutrient provisioning in squamates  
1305 (Hernández-Díaz et al., 2017). In the placenta they found protein expression involved with  
1306 nutrient metabolism, transport, protein synthesis, and embryonic development (Hernández-Díaz  
1307 et al., 2017).

1308

1309 (5) *Uterine glands: adenogenesis, placenta development and histotrophy*

1310 In addition to their role in eggshell deposition in oviparous taxa, uterine glands also secrete  
1311 growth factors and cytokines that support placental development in mammals. In humans, these  
1312 include transforming growth factor- $\beta$  (TGF- $\beta$ ), epidermal growth factor (EGF), vascular  
1313 endothelial growth factor (VECG), and leukemia inhibitory factor (LIF) (Hempstock et al.,  
1314 2004). In eutherians, TGF- $\beta$  supports placental development by regulating proliferation and  
1315 invasion rates of placental cells lines (Caniggia et al., 2000; Hempstock et al., 2004; Lafontaine  
1316 et al., 2011).

1317 Histotrophy (also called histiotrophy) occurs when nutrients are secreted into the uterine  
1318 lumen from vesicles of the columnar epithelial cells of the uterus and taken up by the embryo.  
1319 Histotrophic nutrient provisioning is documented across amniotes including marsupials  
1320 (Whittington et al., 2018), several ungulate taxa (Bazer et al., 2011; Han et al., 2016; Gao et al.,  
1321 2009), humans (Burton et al., 2002), and appear to occur in some viviparous squamates (van  
1322 Dyke et al., 2014). In humans, histotrophic nutrient provisioning occurs during the first trimester.  
1323 The intervillous space is filled with fluid containing uterine gland secretions that get  
1324 phagocytosed by the syncytiotrophoblasts and are the initial nutrient source for the fetus (Burton  
1325 et al., 2002). Two of these glycoproteins are epithelial mucin (*MUC1*) and glycodefin A (*GdA*)  
1326 (Burton et al., 2002). Interestingly, the *MUC15* gene is upregulated during gravidity/gestation in  
1327 the uterus of oviparous and viviparous *Saiphos equalis* individuals (Foster et al., 2020). This also  
1328 occurs in the chorioallantoic placenta of *Pseudemoia entrecasteauxii* during gestation (Griffith et  
1329 al., 2016). Several mucins are expressed in the uterus in non-gravid and gravid samples from  
1330 oviparous individuals of *Lerista bougainvillii* and *Lampropholis guichenoti* (Griffith et al.,  
1331 2016).

1332 A survey of viviparous squamates with modest to extensive placentrophy revealed  
1333 prevalence of histotrophic nutrient provisioning rather than hemotrophy, transfer of nutrients  
1334 between maternal and fetal blood streams (Blackburn 2015). Embryos of *Chalcides chalcides*  
1335 have extensive placentrophy that supports substantial maternal nutrient provisioning and  
1336 histotrophy (Blackburn, 2015a). Histotrophy may lessen parent-offspring conflict and give the  
1337 mother the control over nutrient provisioning compared to hemotrophy (Blackburn, 2015b).

1338 *Chalcides ocellatus* has less extensive placentrophy than *C. chalcides* but the gestating uterus  
1339 still illustrates expression of many genes associated with organic and inorganic nutrient transport

1340 (Blackburn, 2015a). Multiple *TGF-β* genes are differentially expressed in the uterus during  
1341 gestation in *C. ocellatus*, however most these are downregulated compared to non-gestational  
1342 uterine tissue (Murphy et al., 2012). The influence of *TGF-β* on placental development and  
1343 nutrient provisioning in *Chalcides spp.* remains to be explored to my knowledge. A TGF-β  
1344 receptor (*TGFBRI*) was associated with placental development in *Phrynocephalus vlangalii*  
1345 (Gao et al., 2019).

1346 Essential to histotrophy is adenogenesis, the generation of endometrial glands. Adenogenesis  
1347 allows for the secretion of histotrophs. The period of early development during which  
1348 adenogenesis occurs is highly variable among vertebrates but it is required for embryonic  
1349 survival (Gray et al., 2001, 2002; Spencer & Bazer, 2004). Some genes involved with  
1350 adenogenesis in sheep are insulin-like growth factor 1 (*IGF-1*), *IGF-2*, *PAX2*, *LHX1* (also known  
1351 as *LIM1*) and *EMX2*, genes in the abdominal-B HOXA cluster, members of both *Wnt* and  
1352 Hedgehog (*Hh*) gene families (Fazleabas et al., 2004), prolactin (*PRL*), fibroblast growth factor 7  
1353 (*FGF7*), *FGF10*, *FGFR2IIIb*, hepatocyte growth factor (*HGF*), a receptor tyrosine kinase (*c-*  
1354 *Met*), and cadherins (Fazleabas, 2007).

1355 In the gestating uterus of *Chalcides ocellatus*, insulin-like growth factor-binding protein 5  
1356 (*IGFBP5*) is one of the most significantly downregulated genes compared to non-gestational  
1357 uterine tissue (Brandley et al., 2012). *IGFBP5* is evolutionarily conserved and multifunctional,  
1358 with an important role in regulating IGF signaling, including that of *IGF-1* and *IGF-2* (Duan &  
1359 Allard, 2020). Other than adenogenesis in sheep, IGFs serve an important role in the growth of  
1360 fetal and maternal tissues in mammals (Gibson et al., 2001; Kampmann et al., 2019).

1361 Genes involved with histotrophic secretion in the marsupial *Sminthopsis crassicaudata*  
1362 include *AP4SI*, *HYOU1*, and *SRPRA* (Whittington et al., 2018). Nutrient transporters

1363 significantly upregulated at this time are *APOL6* (cholesterol transport (Baardman et al., 2013)),  
1364 *PLA2G10* (hydrolysis of fatty acids during pregnancy (Miele et al., 1987)) and a wealth of SLCs  
1365 (solute carrier proteins for transport of sugar, ions, anions, glucose, fatty acids, calcium and zinc  
1366 (Whittington et al., 2018)). Subsequent research has identified downregulated of *HYOUI* at early  
1367 and mid-gestation; and downregulation of *SRPRA* at mid-gestation in viviparous *Zootoca*  
1368 *vivipara* compared to oviparous (Recknagel et al., 2021a). In a reproductively bimodal skink,  
1369 *Saiphos equalis*, *PLA2G10* is upregulated during viviparous late gestation compared to oviparous  
1370 late gestation (Foster et al., 2020). Upregulation of SLCs also occurs in the viviparous skink  
1371 *Chalcides ocellatus* (Brandley et al., 2012; Van Dyke et al., 2014) and in the uterus during  
1372 pregnancy in the grey short-tailed opossum, *Monodelphis domestica* (Hansen, Schilkey & Miller,  
1373 2016).

1374 Uterine glands are also important for secretions of eggshell precursors. I speculate that genes  
1375 involved with adenogenesis of uterine glands may be similarly used to support histotrophic  
1376 nutrient provisioning during transitions to viviparity, but further research is necessary.

1377 Specialized uterine areolar glands are found in some *Mabuya* lizards, a genus with oviparous  
1378 species and viviparous species that utilize placentrophy and histotrophy (Corso et al., 1988,  
1379 2000; Jerez & Ramírez-Pinilla, 2001; Ramírez-Pinilla, 2006; Vieira et al., 2007; Visser, 1975).

1380 Transcriptomic research focused on histotrophic nutrient provisioning, placental development,  
1381 and secretions of eggshell precursors in oviparous and viviparous *Mabuya spp.* would  
1382 complement literature on the genus.

1383

1384 (6) *Discussion & future directions—embryonic nutrients, gas, and water supply*

1385 Many genes for placental functions in mammals have deep origins in vertebrates (Rawn &  
1386 Cross, 2008). In pairwise comparisons of different viviparous amniotes, there is overlap in  
1387 hormones and proteins (SLC superfamily, insulin-like growth factors, aquaporins and solute  
1388 carrier proteins, etc.) involved in uterine remodeling, placentation, and placental transport. While  
1389 shared genes are recruited to the uterus across viviparous amniotes (Recknagel et al 2021a), there  
1390 are no shared genes recruited to the placenta across viviparous reptiles, mammals, and sharks  
1391 (Foster et al., 2022). Evolutionarily, this suggests higher conservation of the regulatory networks  
1392 associated with uterine responses to viviparity than placental responses to viviparity. The  
1393 relationship of these findings to embryonic nutrient provisioning and the evolution of the  
1394 amniotic egg requires further investigation. Supplementary Table 2 illustrates how genes  
1395 mentioned in text for water, gas, and nutrient transport are expressed in reproductive tissues of  
1396 squamates during gestation and gravidity.

1397 If specific genes or physiological processes impact more than one of the Main Five  
1398 categories, it could have a disproportionate influence on transitions. Such an overlap has already  
1399 been identified in *Zootoca vivipara*, where 11 genes are associated with both eggshell traits and  
1400 gestation length (Recknagel et al., 2021a). The solute carrier (*SLC*) gene superfamily is involved  
1401 with both nutrient transport (Brandley et al., 2012; Whittington et al., 2018) and eggshell  
1402 deposition (Yang et al., 2020). Adenogenesis is essential for histotrophic nutrient provisioning  
1403 and secretion of eggshell precursors. Additionally, progesterone production influences both  
1404 uterine quiescence, which is an important state to maintain in lengthened embryonic retention,  
1405 and it also inhibits hepatic vitellogenesis, an important process for lecithotrophic nutrient  
1406 provisioning. Thus, examining the role of *SLC* gene superfamily members, processes of



1407 adenogenesis, and progesterone production during embryonic development in oviparous and  
1408 viviparous squamate may reveal how interconnectivity of the Main Five are.

1409

## 1410 **V. Embryonic Calcium Provisioning**

1411

1412 The embryonic growth stage requires the greatest demand of calcium (Ecay et al., 2017;  
1413 Packard & Packard, 1984; Stewart & Ecay, 2010). To support this, peak uterine concentrations  
1414 of calcium are highest during either eggshell deposition or during the embryonic growth stage, in  
1415 oviparous and viviparous taxa, respectively (Linville et al., 2010; Stewart et al., 2009).  
1416 Regardless of parity mode, embryonic metabolism drives calcium uptake (Packard & Packard,  
1417 1984). The calcium source(s) utilized have clade-specific implications on the genomic and/or  
1418 physiological changes required to transition between parity modes.

1419

### 1420 *(1) Phylogenetic context of embryonic calcium sources*

1421 Calcium can be acquired by the embryo in three forms: calcium carbonate in the eggshell,  
1422 calcium bound to proteins and lipids in the yolk, and/or free ionic calcium from maternal  
1423 delivery through the placenta (Stewart & Ecay, 2010). These correspond with five calcium  
1424 mobilization patterns: 1) Birds, turtles and crocodiles predominately depend on the eggshell; 2)  
1425 Most squamates, regardless of parity mode, predominately depend on the yolk; 3) Some  
1426 squamate species are reliant on both the eggshell and yolk; 4) Some viviparous squamate species  
1427 are reliant on both the yolk and placenta; and 5) therian mammals and rare viviparous squamates  
1428 predominately depend on the placenta (Blackburn, 2015a; Hoenderop, Nilius, & Bindels, 2005;  
1429 Jenkins & Simkiss, 1968; Kovacs, 2015; Packard, 1994; Packard & Seymour, 1997; Stewart et

1430 al., 2009, 2009; Stewart & Ecy, 2010; Thompson, Stewart et al., 1999; Thompson, Stewart, &  
1431 Speake, 2000; Ramírez-Pinilla, 2006).

1432 From an evolutionary perspective, squamate eggs might serve as the best models of the  
1433 ancestral amniote egg. Unlike birds, oviparous squamates generally rely on yolk calcium rather  
1434 than eggshell calcium. The yolk sac of non-avian reptiles is a good model for the transition  
1435 between the egg of anamniotes and amniotes (Blackburn, 2020). Taken together and given that  
1436 hard calcified eggshells of Archelosaurs are likely derived (as discussed in section III.3)—  
1437 squamate eggs may have the closest resemblance to the ancestral amniote egg. Interestingly, to  
1438 my knowledge, oviparous squamates do not sequester calcium from the eggshell into the yolk  
1439 during incubation (Packard, 1994).

1440

1441 *(2) Hypotheses on calcium mobilization and the evolution of parity modes*

1442 It was hypothesized that predominant reliance on eggshell calcium should constrain lineages  
1443 to oviparity because the evolution of viviparity would result in a lost calcium source (hereafter  
1444 eggshell calcium constraint hypothesis) (Stewart & Ecy, 2010; Packard et al., 1977; Packard &  
1445 Packard, 1984). This hypothesis suggested that viviparity should only evolve in lineages  
1446 predominately reliant on yolk calcium (Packard et al., 1977; Packard & Packard, 1984).  
1447 Fittingly, birds, turtles and crocodilians generally rely on eggshell calcium, and they are  
1448 constrained to oviparity (Anderson et al., 1987). The eggshell calcium constraint hypothesis  
1449 holds true for most viviparous squamates that rely heavily on yolk calcium (Stewart & Castillo,  
1450 1984; Stewart & Ecy, 2010; van Dyke et al., 2014).

1451 Subsequent research revealed that viviparity is not constrained by a prerequisite reliance on  
1452 yolk calcium. Oviparous scincid skinks studied thus far are intermediately reliant on eggshell and

1453 yolk calcium (Linville et al., 2010; Shadrix et al., 1994; Stewart et al., 2009; Stewart &  
1454 Thompson, 1993; Thompson et al., 2001). Calcium placentrophy contributes substantially to  
1455 embryonic development in several viviparous squamates including *Pseudemoia entrecasteauxii*,  
1456 *Eulamprus quoyi*, *Zootoca vivipara*, *Saiphos equalis*, and a species of *Mabuya* lizard (Ecay et al.,  
1457 2017; Linville et al., 2010; Ramírez-Pinilla, 2006; Ramírez-Pinilla et al., 2011; Stewart &  
1458 Thompson, 1993). These taxa, with the exception of *Zootoca vivipara*, are in the family  
1459 Scincidae (Burbrink et al., 2020), which is also the family with the most independent origins of  
1460 viviparity in squamates (Blackburn, 1982, 1999; Pyron & Burbrink, 2014).

1461 To understand the breadth of physiological conditions from which oviparity and viviparity  
1462 evolve in squamates, future research should examine calcium transport in other lineages. Studies  
1463 focused on snakes would be particularly informative given the sparse literature on them.

1464 *Helicops angulatus*, a reproductively bimodal water snake from South America, is an ideal  
1465 model for this (Braz et al., 2016). Thus far, many oviparous snakes are known to be  
1466 intermediately reliant on yolk and eggshell calcium. This has not precluded viviparity from  
1467 evolving in these lineages.

1468 The presence of embryos during extended embryonic retention may trigger positive feedback  
1469 stimuli for continued uterine calcium secretions which may support placental calcium transport,  
1470 and thus incipient calcium matrotrophy (Stewart & Ecay, 2010). This is postulated to resemble  
1471 the hormonal and mechanical stress mechanisms implicated in avian eggshell formation and  
1472 uterine calcium secretions (Bar, 2009a; Stewart & Ecay, 2010). The influx of calcium late in  
1473 viviparous gestation may be triggered in part by embryonic growth that over distends the uterus.  
1474 This is seen in studies on myometrial stretch in mammals when uterine overdistention triggers  
1475 spikes in calcium (Kao & McCullough, 1975; and see e.g. Wray et al., 2015).

1476       Dramatic changes to activity in chorioallantois should not be required during parity mode  
1477 transitions because these homologous tissues (Metcalf & Stock, 1993) transport calcium  
1478 regardless of parity mode (Ecay, Stewart & Blackburn, 2004; Tuan & Scott, 1977; Tuan &  
1479 Knowles, 1984; Tuan et al., 1978, 1986). Specialized placental structures in some viviparous  
1480 squamates enhance calcium provisioning but specialization is not required for placental calcium  
1481 transport (Stewart et al., 2009; Stewart & Ecay, 2010; Thompson et al., 2000). Loss of  
1482 chorioallantoic calcium transporting capacity would be disadvantageous to either parity mode.  
1483 Growing research reveals that, like mammals, placentrophy and viviparity can evolve  
1484 concurrently in squamates (Blackburn, 2015a; Ecay et al., 2017; Stewart & Ecay, 2010).

1485       Placing these previously proposed models in a phylogenetic context, the calcium transport  
1486 method of oviparous ancestors likely has an influence on the method of calcium transport used  
1487 for viviparous taxa—matrotrophic calcium provisioning, lecithotrophic calcium provisioning, or  
1488 a combination of the two. Consistent with the basal cap hypothesis—when viviparity arises from  
1489 oviparous ancestors with embryos that depended predominately on eggshell calcium, this should  
1490 favor a transition to viviparity via incipient calcium matrotrophy because the chorioallantois  
1491 already plays the major role in transporting calcium from the eggshell to the embryo. Since the  
1492 reproductive mode and calcium provisioning of oviparous ancestors are essentially unknown,  
1493 researchers can use the closest oviparous relatives as proxies. Similarly, viviparous taxa that are  
1494 in close phylogenetic proximity to oviparous taxa that depend on lecithotrophic calcium  
1495 provisioning should remain reliant on yolk calcium. Together, these guidelines provide a  
1496 framework from which researchers can form hypotheses about the calcium provisioning method  
1497 of a viviparous lineage if the calcium provisioning method of oviparous close relatives are  
1498 known, or vice versa. Measurements of the proportional contribution of different calcium sources

1499 during development has only been done in select taxa (e.g. Packard, 1994; Stewart, 2013;  
1500 Stewart & Ecy, 2010; Stewart, Ecy & Blackburn 2004). Once validated, the framework (i.e.,  
1501 the calcium provisioning method of close relatives) can help increase the speed at which science  
1502 measures and infers the evolutionary history of calcium provisioning across amniotes and  
1503 squamates. Collection of this data across the squamate phylogeny may enable assignment of  
1504 these hypotheses to specific clades.

1505 Embryonic calcium source could have implications on the physiological changes required to  
1506 transition between parity modes. Reliance on yolk calcium should render, essentially, no  
1507 mechanistic changes for calcium transport. On the other hand, incipient calcium matrotrophy  
1508 requires regulatory changes in the uterus, like timing of calcium secretions (Griffith et al., 2015).  
1509 However, regardless of parity mode 1) the uterus secretes calcium, 2) the chorioallantois  
1510 transports calcium and 3) embryonic metabolism drives uptake of calcium. Assuming maternal  
1511 tissue remains responsive to embryonic metabolism, the joint evolution of matrotrophic calcium  
1512 provisioning with viviparity may require little to no physiological adjustments.

1513 The diversity of embryonic calcium provisioning patterns in viviparous squamates may not  
1514 be fully explained by the eggshell calcium constraint hypothesis (Packard et al., 1977; Packard &  
1515 Packard, 1984) or incipient calcium matrotrophy (Stewart & Ecy, 2010). Both hypotheses  
1516 implicitly assume that viviparity equates to a lost eggshell. In one viviparous squamate, *Haldea*  
1517 *striatula*, and in viviparous populations of two reproductively bimodal lizards, *Zootoca vivipara*  
1518 and *Saiphos equalis*, the calcified eggshell is considered as a component of the placenta (Stewart,  
1519 2013). Some other viviparous squamates have transient calcified patches on their embryonic  
1520 membranes (Blackburn, 1998; Heulin, 1990, 2005; Qualls, 1996) suggesting that uterine calcium  
1521 secreting capabilities in early gestation may be retained in some viviparous lineages. In the case

1522 of reversals, it remains unknown how the uterus shifts back to early calcium secretions after  
1523 ovulation (Blackburn, 2015b; Griffith et al., 2015).

1524

1525 *(3) Embryonic calcium provisioning mechanisms*

1526 In vertebrates, specialized tissues that recover environmental calcium and transport it into  
1527 blood circulation maintain conserved mechanisms for intracellular calcium transport (Bronner  
1528 2003; Hoenderop et al., 2005). These include the uterus, chorioallantoic tissues, and yolk  
1529 splanchnopleure (Bronner, 2003; Hoenderop et al., 2005; Stewart, 2013). Therefore, uterine and  
1530 embryonic tissues may be pre-adapted for maternal and embryonic calcium provisioning.

1531 In birds, a sub-compartment of the mammillary layer of the eggshell is the calcium reserve  
1532 body (Chien et al., 2009), which contains microcrystals of calcite that get dissolved and  
1533 transported as calcium to the embryo (Chien et al., 2009). Calcium is eroded from the eggshell  
1534 by acid released from villus cavity cells (VCCs) in chorioallantoic membrane (Anderson, Gay,  
1535 and Schraer, 1981; Narbaitz et al., 1981; Packard & Lohmiller, 2002; Simkiss, 1980). This  
1536 increases the carbonic anhydrase activity of the cells enabling calcium to be released into the  
1537 cavity between the eggshell and the chorionic epithelium, where it is taken up by capillary  
1538 covering cells (CCCs) in chorioallantoic membrane (Coleman & Terepka, 1972). In some  
1539 species this erosion leads to a gradual weakening of the eggshell that facilitates hatching (Chien,  
1540 Hincke & McKee, 2008). In chickens, transcalcin, a calcium binding protein, is credited for the  
1541 calcium transporting capacity of the chorioallantoic membrane (Tuan & Knowles, 1984; Tuan &  
1542 Ono, 1986; Tuan & Scott, 1977; Tuan et al., 1978, 1986). The presence of VCCs and CCCs in  
1543 the chorioallantois of viviparous squamates would indicate a known route through which calcium  
1544 can be absorbed.

1545 Transcellular calcium transport has been modeled as a three-step process involving proteins  
1546 calbindin-D9K, calbindin-D28K, and the highly calcium-specific ion channels of the transient  
1547 receptor potential vanilloid gene family (*TRPV5* and *TRPV6*) (Stewart & Ecaj, 2010). Across  
1548 vertebrates, this machinery is shared in epithelial tissues with significant roles in calcium  
1549 transport (Hoenderop et al., 2005). Estrogen and vitamin D3 have regulatory roles in this  
1550 process.

1551 Calbindin-D9K, calbindin-D28K, *TRPV5*, and *TRPV6* is involved with calcium exchange in  
1552 multiple organs of birds, squamates, and mammals. Broadly, activity of calbindin-D9K and/or  
1553 calbindin-D28K is associated with patterns of calcium absorption in the mammalian kidney and  
1554 uterus (Bindels, 1993; Luu et al., 2004), murine uterus and placenta (Lafond & Simoneau, 2006;  
1555 Koo et al., 2012), and chicken duodenum and uterus (Bar, 2009b; Yang et al., 2013). In humans,  
1556 calbindin-D9K and calbindin-D28K are critical to the active transport of Ca<sup>2+</sup> across placental  
1557 cells (Faulk & McIntyre, 1983; Belkacemi, Simoneau & Lafond, 2002; Belkacemi et al., 2004).  
1558 A study on rats suggests that calbindin-D9K increases by over 100-fold in the last 7 days of  
1559 gestation (Glazier et al., 1992), when the embryo gains the majority of calcium. *TRPV6* is  
1560 involved with maternal-fetal calcium transport in mice (Suzuki et al., 2008). Increased *TRPV6*  
1561 and calbindin-D28K expression occurs during eggshell formation in chickens (Yang et al.,  
1562 2013). Given the involvement of these genes in both eggshell deposition and embryonic calcium  
1563 transport, squamates may have exploited this pathway to support transitions. Expression of these  
1564 genes during gestation or gravidity in squamates has been detected (e.g. calbindin-d9K in  
1565 *Saiphos equalis*, and calbindin-d28k in *Zootoca vivipara*) (Foster et al., 2020; Recknagel et al.,  
1566 2021a), and is expanded upon in the following paragraphs.

1567 In several highly matrotrophic lizards, embryonic uptake of calcium is associated with  
1568 placental expression of calbindin-D28K (Stewart et al., 2009; Stinnett et al., 2011, 2012). In both  
1569 oviparous and viviparous embryos of *Zootoca vivipara*, sharp increase in calcium uptake in late  
1570 development coincides with increased calbindin-D28K and PMCA by the chorioallantois  
1571 (Stewart et al., 2009, 2011). In oviparous corn snakes, *Pantherophis guttatus*, expression of  
1572 calbindin-D28K in the yolk-sac and chorioallantoic membrane coincides with growth of these  
1573 tissues and calcium transport activity (Ecay et al., 2004). The chorioallantois of other lizards and  
1574 snakes transport calcium to the embryo and express calbindin-D28K and PMCA (Blackburn,  
1575 2004; Ecay et al., 2004; Stewart et al., 2010; Stinnett et al., 2012).

1576 Viviparous embryos of *Zootoca vivipara*, a reproductively bimodal lizard, incubated *ex utero*  
1577 respond to availability of calcium by increasing expression of calbindin-D28K (Ecay et al.,  
1578 2017). In this species, embryonic recognition of environmental calcium stimulates a transcellular  
1579 calcium transporting mechanism and may also alter chorioallantoic membrane paracellular  
1580 permeability to calcium (Ecay et al., 2017). The authors proposed that there is a calcium sensing  
1581 receptor (CaSR) on chorionic epithelial cells to support this in both oviparous and viviparous  
1582 *Zootoca vivipara* embryos (Ecay et al., 2017), similar to the CaSRs expressed by vertebrate cells  
1583 involved in calcium homeostasis (Brennan et al., 2013).

1584 As mentioned earlier, PMCA activity is associated with eggshell deposition in birds and  
1585 oviparous squamates (Bar, Rosenberg, & Hurwitz, 1984; Hincke et al., 2012; Wasserman et al.,  
1586 1991). PMCA is also crucial for calcium transport in late embryonic development in rats (Glazier  
1587 et al., 1992). In viviparous scincid lizards, *Niveoscincus metallicus*, *N. ocellatus*, and  
1588 *Pseudemoia spenceri*, PMCA was expressed in uterine glandular and surface epithelia during  
1589 pregnancy but only *P. spenceri* expressed it throughout gestation (Herbert et al., 2006). When



1590 PMCA was not detected by immunoblotting in the yolk splanchnopleure of *Haldea striatula*, a  
1591 viviparous snake that relies predominately on yolk calcium (Stewart, 1989; Fregoso, Stewart, &  
1592 Ecay, 2010), NCXs were proposed as an alternative transporter of calcium (Fregoso et al., 2012).  
1593 NCXs are important for placental calcium transport in humans (Belkacemi et al., 2005).

1594        Calcitropic hormones, those involved with calcium transport, and phosphotropic hormones,  
1595 those involved with phosphorous transport, operate via an interconnected pathway (Andrukhova  
1596 et al., 2016; Biber, Hernando & Forster, 2013; Blaine, Chonchol & Levi, 2015; Erben &  
1597 Andrukhova, 2015). Phospho- and calcitropic hormones are important regulators of fetal serum  
1598 mineral concentrations (Kovacs, 2015). Evidence from viviparous amniotes suggests that these  
1599 are suitable candidates for embryonic calcium provisioning. In mice, genes encoding parathyroid  
1600 hormone (*PTH*) and *PTH*-related peptide (*PTHrP*) are important regulators of placental calcium  
1601 transport (Kovacs et al., 1996; Simmonds et al., 2010). A non-exhaustive list of additional  
1602 candidates for embryonic calcium provisioning include fibroblast growth factor 23 (Bar, 2009a;  
1603 Erben & Andrukhova, 2015; Stewart & Ecay, 2010), the annexin gene family (Matschke et al.,  
1604 2006), carbonic anhydrase (Narbaitz et al., 1981; Tuan & Knowles, 1984), and calcium binding  
1605 proteins (CaBPs) can be found in the referenced literature.

1606

#### 1607        (4) *Discussion & future directions—calcium provisioning and parity mode evolution*

1608        Phylogenetic frameworks enable researchers to make broader testable hypotheses about the  
1609 evolutionary history of calcium provisioning in specific clades. Such a framework is proposed in  
1610 section V.2 to infer ancestral parity modes in the context of calcium provisioning in amniotes.  
1611 Implications gleaned from taxon-specific studies can be explored in distantly related analogous  
1612 groups.

1613 Genes involved with calcium transport in uterine and embryonic tissues have been described  
1614 across mammals, birds, and reptiles. Like other amniotes, activity of calbindin-D28K and PMCA  
1615 supports embryonic calcium provisioning across diverse oviparous and viviparous squamates.  
1616 Their involvement with both eggshell deposition and embryonic calcium provisioning makes  
1617 these particularly interesting candidates for parity mode evolution. The regulatory influence of  
1618 other molecules in calcium transport, like *PTH*, *PTHrP* and NCXs has not been evaluated  
1619 thoroughly in squamates. Additional reviews on mechanisms of embryonic calcium provisioning  
1620 in squamates can be found in the literature (Stewart, 2013; Stewart & Eday, 2010).

1621 Additionally, I add a speculation. Perhaps lineages with incipient calcium matrotrophy more  
1622 feasibly reverse to oviparity because of the continued role of the uterus in calcium provisioning.  
1623 However, this hypothesis only holds up if maternal provisioning of calcium is not synonymous  
1624 with maternal provisioning of all nutrients.

1625

## 1626 **VI. Maternal-Fetal Immune Dynamics**

1627

1628 Medawar (1953) pointed out the paradigm between the peripheral body's normal attack  
1629 response to allografts (foreign tissue) and uterine tolerance to embryos (Medawar, 1953). This  
1630 was inspired by earlier work by Ray Owen (Owen, 1945). Stricter regulation of the maternal and  
1631 fetal immune systems is expected for viviparous reproduction because of contact between uterine  
1632 and embryonic tissues. Oviparity may pose less of an immunological challenge. Medawar  
1633 suggested barriers, inertness and/or immunosuppression enable pregnancy. This formed the  
1634 foundation of decades of medical research on immune dynamics between maternal, embryonic,  
1635 and paternal immune factors in utero.

1636 In recent years, there was a call for a reappraisal of Medawar's paradigm (Chaouat, 2010,  
1637 2016; Moffett & Loke, 2004, 2006; Mor et al., 2011; Stadtmayer & Wagner, 2020b; Yoshizawa  
1638 2016). Moffett & Loke (2006) caution against conceptualizing embryos as analogs of allografts.  
1639 To my knowledge, this perspective has yet to reach the evolutionary literature on squamate  
1640 parity mode evolution (Foster et al., 2020; Graham et al., 2011; Gao et al., 2019; Murphy &  
1641 Thompson, 2011; van Dyke, Brandley, & Thompson, 2014; Murphy, Thompson, & Belov, 2009;  
1642 Recknagel et al., 2021a). Importantly, challenges to Medawar's paradigm do not preclude  
1643 immunological responses to viviparity. They simply suggest that the immune environment of the  
1644 uterus is uniquely evolved to support exposure to foreign tissue.

1645 The uterine immune system has a distinct evolutionary history from the periphery. It enables  
1646 cooperative dynamics with foreign tissues. It supports fertilization and early embryonic  
1647 development. This should have started evolving, distinct from the periphery, since internal  
1648 fertilization first originated. To contextualize this, I discuss the changing landscape of  
1649 immunological research at the maternal-fetal interface and what it means in the context of  
1650 amniote parity mode evolution. Overall, I hope readers consider how the uterus evolved to  
1651 support internal gestation, and which model systems may be appropriate to investigate this.

1652 Most literature on maternal-fetal immune dynamics limits itself to mammals. Squamates may  
1653 serve as a better comparative model for understanding the evolution of the uterine immune  
1654 system. Active research on the peripheral reptilian immune system (Zimmerman et al., 2010,  
1655 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et al., 2017;  
1656 Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights on this.

1657

1658 *(1) Comparing amniote immune systems*

1659 Cellular components of the innate immune system are conserved across jawed vertebrates  
1660 (Uribe et al., 2011; Zimmerman et al., 2010). The general machinery of the adaptive immune  
1661 system is ancient despite divergences and convergences across all domains of life (Ghosh et al.,  
1662 2011; Morales et al., 2017; Müller et al., 2018; Rimer et al., 2014). Diversification of antigen  
1663 receptor genes likely occurred independently in a lineage-specific fashion (Boehm et al., 2018).  
1664 Compared to mammals, the avian immune system requires less antigen (Larsson et al., 1998).  
1665 Birds also have faster but shorter antibody responses, potentially due to their higher body  
1666 temperatures (Zimmerman, 2010).

1667 Reptiles have the same general components of the mammalian immune system (Zimmerman,  
1668 2020). However, the reptilian immune system may not fit neatly into the two arms of mammalian  
1669 immune systems—innate and adaptive (Zimmerman, 2010; 2020). Expanding upon this is  
1670 beyond the scope of this review, but it is worth considering in future evolutionary research.  
1671 Squamates may serve as a better comparative model for understanding the evolution of the  
1672 uterine immune system. Active research on the peripheral reptilian immune system (Zimmerman  
1673 et al., 2010, 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et  
1674 al., 2017; Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights. I  
1675 refer readers to articles by Zimmerman et al. (2010, 2020) and Ghorai et al. (2018), and the book  
1676 by Williams (2012) for more information on the avian immune system.

1677

## 1678 (2) *Medawar's paradigm*

1679 Tolerance toward the foreign fetus was postulated to occur through immunological inertness,  
1680 immunosuppression or immunotolerance mechanisms (Medawar, 1953). Theoretically,  
1681 immunotolerance could be established if there are relatively small quantities of alloantigens

1682 present, resulting in regulatory responses rather than activating responses (Pradeu, 2011).  
1683 Contradicting this, the larger the alloantigen difference between the mother and embryo the  
1684 bigger and healthier the placenta is in rats (Chaouat et al., 2010). In humans, divergent HLA  
1685 profiles between mother and embryo do not lead to detrimental immune responses (Tilburgs,  
1686 Scherjon, & Claas, 2010). Instead, cooperative inflammatory responses between maternal and  
1687 fetal tissues support reproduction (Stadtmauer et al., 2020a). In humans, microchimeric cell  
1688 populations, presence of cells from one individual in another genetically distinct individual, are  
1689 now considered a normal expectation of pregnancy (Nelson, 2012).

1690 In his 1991 Nobel Lecture, Medawar acknowledged that maternal and embryonic tissues  
1691 have regular exposure to alloantigens (Medawar, 1991). It has become clear that the maternal  
1692 immune system actively responds to fetal alloantigen rather than responding solely with  
1693 ignorance or anergy (Arck & Hecher, 2013). Neither maternal immunosuppression/privilege nor  
1694 embryonic inertness/immaturity fully explain immune dynamics during gestation in mammals,  
1695 including those with the simple epitheliochorial placentation (Chaouat et al., 2010; Chavan,  
1696 Griffith & Wagner, 2017; Moffett & Loke, 2004, 2006; Stadtmauer & Wagner, 2020a).

1697

### 1698 *(3) Perspectives on the evolution of the uterine immune system*

1699 Viviparous reproduction existed eons before the origin of mammals and, to my knowledge,  
1700 no evidence suggests there was immune conflict within these taxa (Chaouat, 2016). Placentrophly  
1701 existed as far back as the invertebrate clade Bryozoa (Ostrovsky, 2013; Schwaha et al., 2019),  
1702 suggesting an ancient history for supportive maternal-fetal immune dynamics. Differing from  
1703 Medawar's paradigm, Polly Matzinger, who proposed the 'danger model' for the immune system

1704 (Matzinger, 2007), wrote “Reproduction cannot be a danger. It does not make evolutionary  
1705 sense” (Chaouat, 2016).

1706 In mammals, immunological cells at the maternal-fetal interface may not function through  
1707 self-non-self-discrimination, as they are understood to function in the rest of the body (Chaouat,  
1708 2016; Moffett & Loke 2004, 2006). The ‘maternal-fetal interface’ may be better conceptualized  
1709 as ‘maternal-fetal intra-action’ given the dynamics between maternal and fetal immune systems  
1710 in mammals (Yoshizawa, 2016). It is unclear if these insights apply to other viviparous amniotes.

1711 In mammals, immune factors in the uterus and placenta appear to be specifically evolved to  
1712 support maternal-fetal immune dynamics. Several cell types have unique functions and/or  
1713 phenotypes in utero—uterine NK (uNK) cells, uterine macrophages, uterine T regulatory cells  
1714 (Faas & de Vos, 2017; Mold et al., 2008, 2010; Mold & McCune, 2011). An immunosuppressive  
1715 antigen, HLA-G, is almost exclusively expressed by trophoblasts (Faulk & Temple, 1976;  
1716 Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al., 1997). Taken from an  
1717 evolutionary perspective, this suggests that the uterine immune system in viviparous mammals  
1718 evolved unique responses to allogenic tissues that differ from the periphery. Whether the  
1719 evolution of this system predates mammals remains to be explored, to my knowledge.

1720 It is suggested that viviparous reproduction is immunologically compatible in species with  
1721 less active adaptive immune system, like sharks (Chaouat, 2016). In these clades, innate immune  
1722 cells, like uNK cells, may be sufficient to regulate immune responses during pregnancy (Moffett  
1723 & Loke, 2004; Chaouat, 2016). Given that there is an unclear distinction between the innate and  
1724 adaptive immune system in reptiles (Zimmerman, 2020), determining immunological difficulty  
1725 of evolving viviparity in squamates requires further investigation.

1726 In uterine tissue of oviparous and viviparous skinks maternal antigens are expressed prior to  
1727 and during gestation and gravidity (Murphy et al., 2009), but the viviparous species in the study  
1728 have a unique expression profile of MHC antigens which may ‘hide’ the embryo from the  
1729 maternal immune system (Murphy et al., 2009). Similarly, in a reproductively bimodal skink,  
1730 *Saiphos equalis*, both oviparous and viviparous gestation is associated with expression of MHC  
1731 genes (Foster et al., 2020). Regardless of parity mode, *S. equalis* expresses genes associated with  
1732 immunocompetence, including MHC genes including *H2-EA* (Foster et al., 2020). The similar  
1733 profile between the oviparous and viviparous state is attributed to the use of very long egg  
1734 retention utilized by oviparous *S. equalis* (Foster et al., 2020). This highlights that extended  
1735 embryonic retention is accompanied with immunological responses in utero, which is relevant to  
1736 the EER model on amniote origins.

1737 Some of these genes expressed by *S. equalis* are also expressed in viviparous *Chalcides*  
1738 *ocellatus* during gestation including complement component genes (C3, C9) and MHC genes  
1739 (Brandley et al., 2012; Foster et al., 2020). The majority of immune genes expressed during  
1740 gestation/gravidity in *S. equalis* have immunoglobulin receptor binding functions (Foster et al.,  
1741 2020), an important feature of eutherian pregnancy that prevents rejection of the fetus through  
1742 actions of the maternal innate immune system (Alijotas-Reig, Llorba, Gris, 2014)). In another  
1743 reproductively bimodal skink, *Zootoca vivipara*, immune system response genes are enriched in  
1744 the set of genes under divergent selection in oviparous and viviparous genomes (Recknagel et al.,  
1745 2021a).

1746

1747 (4) *Implications of the reptilian immune system and morphology on parity mode evolution*

1748 Ectothermic reptiles may inherently have a more tolerogenic uterine environment compared  
1749 to mammals due to their slower antibody response. It can take up to six weeks to reach peak  
1750 concentrations (Ingram & Molyneux, 1983; Grey, 1963; Marchalonis et al., 1969; Pye et al.,  
1751 2001; Origgi et al., 2001; Work et al., 2000). A slower metabolism also makes several reptiles  
1752 more tolerogenic to pathogens (Ghorai & Priyam, 2018).

1753 During pregnancy in the viviparous skink, *Chalcides ocellatus*, there is a reduced response to  
1754 in vitro exposure to mitogens concanavalin A (Con A), phytohemagglutinin (PHA), and  
1755 *Escherichia coli* lipopolysaccharide (LPS) (Saad & El Deeb, 1990). Oviparous lizards exhibit  
1756 immune activation tradeoffs during reproductive cycles (Cox, Peadar, & Cox, 2015; Durso &  
1757 French, 2018; French, Johnston, & Moore, 2007; Uller, Isaksson, & Olsson, 2006).

1758 In the majority of viviparous squamates, the eggshell membrane is absorbed during  
1759 pregnancy (Blackburn, 1993). In mammals, epitheliochorial placentation (the most superficial  
1760 and non-invasive placenta type) is sufficient to cause immunorecognition from the mother.  
1761 Specialized placental cells, trophoblasts, may be more common in other viviparous vertebrates  
1762 than previously recognized (Blackburn, 2015a). For example, a gene with fusogenic properties  
1763 characteristics of trophoblast syncytins was recently identified in the *Mabuya* lizard placenta  
1764 (Cornelis et al, 2017). In mammals, trophoblasts are antigen presenting and actively participate  
1765 in maternal-fetal immune dynamics.

1766 A few viviparous squamates have placentas with characteristics similar to placentas found in  
1767 eutherian mammals—syncytialized cells layers, specialized zones such as areolae and  
1768 placentomes, or cellular invasion of maternal tissues by the fetus (Blackburn & Flemming, 2012;  
1769 Jerez & Ramírez-Pinilla, 2001; Vieira et al., 2007). The increased contact here may require more



1770 tightly regulated immune dynamics at the maternal-fetal interface compared to other viviparous  
1771 squamates.

1772

1773 (5) *The inflammation paradox*

1774 In mammals, implantation evolved from an ancestral inflammatory attachment reaction  
1775 (Griffith, Chavan et al., 2017). Inflammation is the most crucial system to support implantation,  
1776 but it is also the greatest threat to the continuation of pregnancy (Chavan et al., 2017). This  
1777 phenomenon is called the inflammation paradox. In humans, immune cells including uterine  
1778 macrophages, T cells of multiple subtypes, uterine natural killer (uNK) cells, dendritic cells, and  
1779 natural killer T (NKT) cells increase until implantation and remain abundant in the uterus  
1780 throughout first trimester (Bulmer et al., 1991; Bulmer, Williams & Lash, 2010). Early  
1781 implantation in humans is characterized by high pro-inflammatory T helper (Th)-1 cells and  
1782 cytokines (IL-6, IL-8, and TNF $\alpha$ ) (Yoshinaga, 2008). The exploitation of inflammatory  
1783 mechanisms for eutherian implantation and the shift toward non-inflammatory activity to  
1784 maintain pregnancy may have been key in enabling extended embryonic retention of eutherians  
1785 (Griffith, Chavan et al., 2017).

1786 How the inflammation paradox applies to viviparous squamates is unclear, given that  
1787 placentation in squamates and mammals is not homologous (Griffith, Van Dyke, & Thompson,  
1788 2013). In extrauterine pregnancies of mammals with non-invasive placentas, the embryo will  
1789 invade extrauterine tissue because it is not inhibited by uterine secretions (Vogel, 2005; Samuel  
1790 & Perry, 1972). However, in *Pseudemoia entrecasteauxii*, a viviparous skink that also has a non-  
1791 invasive placenta, extrauterine pregnancy does not result in invasive implantation of extrauterine  
1792 tissues (Griffith, Van Dyke, & Thompson, 2013). The inherent invasive nature of mammalian

1793 embryos outside of the uterus, compared to the non-invasive nature of viviparous squamate  
1794 embryos studied thus far, suggests that the parent-offspring conflict and the inflammation  
1795 paradox may be less pronounced in viviparous squamates compared to viviparous mammals.

1796

1797 *(6) Inertness and barriers at the maternal-fetal interface*

1798 The uterine environment is not inert or sterile (Agostinis et al., 2019; Erlebacher, 2013;  
1799 Moffett & Loke, 2006; Munoz-Suano, Hamilton, & Betz, 2011; Murphy, Thompson, & Belov,  
1800 2009; Yoshimura, Okamoto, & Tamura, 1997). In humans, the decidual layer of the uterus  
1801 during pregnancy is comprised of ~40% leukocytes (Ander, Diamond, & Coyne, 2019; Manaster  
1802 & Mandelboim, 2010). This cellular subpopulation has 70% uNK cells, 10-20% antigen  
1803 presenting cells (APCs) including macrophages and dendritic cells, and 3-10% T cells of several  
1804 subtypes (Abrahams et al., 2004; Hanna et al., 2006; Kämmerer et al., 2006; Le Bouteiller &  
1805 Piccinni, 2008; Liu et al., 2017; Manaster & Mandelboim, 2010; Moffett-King, 2002; Moffett &  
1806 Loke, 2006; Roussev et al., 2008). There is an abundance of decidual large granular lymphocytes  
1807 (LGLs), CD3-NK cells and CD3+ activated cytotoxic T cells, in the human uterus, that have  
1808 cytotoxic properties and produce cytokines, and these are affected by fetal MHC molecules  
1809 (Rieger, 2002).

1810 Birds also have immunocompetent cells in their oviducts. T and B cells are present in  
1811 chicken ovary where they are stimulated by estrogen (Barua & Yoshimura, 1999; Withanage et  
1812 al., 2003; Zettergren & Cutlan, 1992). Other immunocompetent cells in the chicken oviduct  
1813 include IgG+, IgA+ and CD3+ (Yoshimura, Okamoto, & Tamura, 1997). Immune competent  
1814 cells located throughout the mucosal tissue of avian oviductal segments including macrophages,

1815 antigen presenting cells (APCs) expressing MHC class II antigens, helper T cells and cytotoxic T  
1816 cells, and premature B cells (Das, Isobe, & Yoshimura, 2008).

1817 Inert barriers between maternal and fetal tissues may 'hide' the embryo. In oviparous taxa,  
1818 the eggshell may serve as a barrier. However, the antimicrobial properties of the eggshell matrix  
1819 in birds demonstrate that even the eggshell is not inert. The FAS ligand, also called APO-1 or  
1820 CD95, in humans and rodent embryonic tissue was proposed to serve as a barrier because it  
1821 causes apoptosis of surrounding maternal immune cells (Kayisli et al., 2003; Makrigiannakis et  
1822 al., 2008).

1823 Medawar suggested that an impermeable placenta strictly regulates molecular exchanges,  
1824 preventing rejection of the embryo (Medawar, 1991). Syncytiotrophoblasts lack cellular junctions  
1825 and thus it was postulated to serve as this barrier (Ander et al., 2019). However, the growing data  
1826 on bidirectional cellular traffic of APCs, even in mammals with noninvasive placentas, rejected  
1827 this hypothesis (Bakkour et al., 2014; Burlingham & Bracamonte-Baran, 2015; Fujiki et al.,  
1828 2008; Turin et al., 2007).

1829

### 1830 (7) *T cell populations and mammalian viviparity*

1831 In mammals, immune-dynamics at the maternal-fetal interface are established through  
1832 innate and adaptive immune responses. There is a delicate balance between ratios of Th1, Th2,  
1833 Th17, Tregs and memory T cells at the maternal-fetal interface in eutherian mammals during  
1834 gestation (Chaouat et al., 1997; Kieffer et al., 2019; Peck & Mellins, 2010; Saito et al., 2010; Wu  
1835 et al., 2014). A shift in utero from T helper type 1 (Th1) cells to T helper type 2 (Th2) cells  
1836 during gestation in mammals equates to a shift from pro-inflammation to anti-inflammation. The  
1837 galectin proteins, GAL-13 and GAL-14, expressed by syncytiotrophoblasts, bind to T cells

1838 where they inhibit activation, induce apoptosis, and enhance interleukin-8 (IL-8) production  
1839 (Balogh et al., 2019).

1840 Growing research is revealing the central role of Tregs at the maternal-fetal interface  
1841 during pregnancy in mammals (Teles et al., 2013; Wienke et al., 2019). Tregs play a central role  
1842 in immunosuppression in mammals (Attias, Al-Aubodah, & Piccirillo, 2019). Differentiation of  
1843 Tregs is governed by the transcription factor, *FOXP3* (Ramsdell & Rudensky, 2020).  
1844 Alloantigen-dependent, uterine T cell signaling, and immunocompetent embryonic cells and their  
1845 products facilitate enhanced regulatory phenotypes of immune cells overall (Ander et al., 2019).

1846 The T-cell dependent adaptive immune system of mammals is unique. This may have  
1847 prompted their intricate balance of Treg mediators of immunotolerance at the maternal-fetal  
1848 interface (Chaouat, 2016). Birds rely more heavily on B cells. In non-avian reptiles, T helper  
1849 cells are functional, but the presence and function of other T cell subsets is unclear (Zimmerman,  
1850 2020; Zimmerman, Vogel, & Bowden, 2010). The potential role of T cells and Tregs in  
1851 viviparous squamate gestation should not be discounted. Treg-like cells have been identified in a  
1852 pufferfish, *Tetraodon nigroviridis* (Wen et al., 2011), suggesting that Tregs may have an ancient  
1853 evolutionary history.

1854

#### 1855 (8) *Progesterone, cytokines, and maternal-fetal immune dynamics*

1856 In addition to the role of progesterone in uterine quiescence (embryonic retention) and  
1857 hepatic vitellogenesis (nutrient provisioning), it also plays a role in maternal-fetal immune  
1858 dynamics. In the uterus of pregnant mammals, progesterone concentrations are associated with  
1859 altered B cell immunoglobulin secretion, inhibition of NK-cell mediated cytotoxicity and the shift  
1860 from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) dominated immune responses

1861 (Druckmann & Druckmann, 2005). Progesterone is also associated with immunomodulatory  
1862 effects (Ortega Brown et al., 1990). During gestation in *Agkistrodon piscivorus*, a viviparous pit  
1863 viper, progesterone concentrations are associated with decreased complement performance  
1864 (Graham et al., 2011), a portion of the immune system that promotes inflammation, among other  
1865 immune functions.

1866 In humans, progesterone induced protein (PIBF) is transported by placental extravillous  
1867 trophoblasts to maternal lymphocytes causing the induction of interleukin-10 (IL-10) production,  
1868 contributing to the Th2 dominant responses (Szekeres-Bartho, Šučurović, & Mulac-Jeričević,  
1869 2018). IL-10 is a potent anti-inflammatory cytokine that is produced by multiple cell types  
1870 (Zimmerman, Bowden, & Vogel, 2014). It is associated with Th2 response, and it inhibits Th1  
1871 responses. The phenotype of uterine macrophages is affected by trophoblasts when they secrete  
1872 IL-10 and macrophage colony-stimulating factor (M-CSF) (Svensson-Arvelund et al., 2021). IL-  
1873 10 inhibits IFN- $\gamma$  and increases in response to infection in chickens (Giansanti, Giardi, & Botti,  
1874 2006; Rothwell et al. 2004). In the uterus of the oviparous skink, *Lampropholis guichenoti*,  
1875 during gravidity and non-gravidity, IL-10 is expressed (Griffith et al., 2016).

1876 Proinflammatory cytokines may be downregulated during reproductive periods to limit  
1877 maladaptive immune responses to the foreign fetus (Zimmerman, Vogel, & Bowden, 2010). In  
1878 mammals, IL-1 allows release of hormones in human trophoblasts (Petraglia et al., 1990;  
1879 Masuhiro et al., 1990; Yagel et al., 1989), facilitates implantation (Haimovici, Hill, & Anderson,  
1880 1991; Hill, 1992; Tartakovsky & Ben-Yair, 1991), and influences the initiation of labor (Romero  
1881 et al., 1989, 1992). Regulation of the proinflammatory cytokines tumor necrosis factor (TNF)  
1882 and interleukin 1B (IL-1 $\beta$ ) is of particular importance in eutherian pregnancy (Haider & Knöfler,  
1883 2009; Paulesu, Romagnoli, & Bigliardi, 2005; Saito et al., 2010; Tayade et al., 2006).

1884 The uterine tissue of two reproductively bimodal squamates—viviparous individuals of  
1885 *Chalcides chalcides*, and oviparous and viviparous individuals of *Zootoca vivipara*—express IL-  
1886 1 $\beta$  (Paulesu et al., 1995, 2005; Romagnoli et al., 2003). In the uterus of the viviparous skink,  
1887 *Pseudemoia entrecasteauxii*, during gestation regulation of TNF and IL-1 $\beta$  at the transcriptional  
1888 and post-translation levels, respectively, may reduce inflammation (Hendrawan et al., 2017). The  
1889 pro-inflammatory function of IL-1 $\beta$  in *Pseudemoia entrecasteauxii* may play a role developing a  
1890 more complex placenta (Hendrawan et al., 2017). The placenta of *Chalcides chalcides* expresses  
1891 pro-inflammatory cytokines, IL-1 $\alpha$  and IL-1 $\beta$ , at specific times during gestation (Paulesu et al.,  
1892 1995). During gestation, *Chalcides ocellatus* also differentially expresses 27 other interleukins  
1893 and interleukin related products (Brandley et al., 2012).

1894 The expression of IL-34 in a marsupial, the fat-tailed dunnart, during pre-implantation  
1895 (Whittington et al., 2018) may have an immunosuppressive function to help tolerate potential  
1896 contact of maternal and fetal tissues when the embryonic shell coat disintegrates (Lindau et al.,  
1897 2015). In chickens, IL-34 regulates Th1 and Th17 cytokine production (Truong et al., 2018).  
1898 During gestation in *Pseudemoia entrecasteauxii*, IL-16 and IL-1 $\alpha$  are expressed in addition to  
1899 three receptors for Th17 family cytokines—IL-17RA, IL-17RC, and IL-17RA (Griffith,  
1900 Brandley, et al., 2016, 2017). In the yolk sac of *Pseudemoia entrecasteauxii* during pregnancy  
1901 interleukin related molecules, *ILDR1*, *IRAK1*, and *SIGIRR*, are differentially expressed (Griffith  
1902 et al., 2016). This profile suggests the presence of tricellular tight junctions and/or tricellulin  
1903 (Higashi et al., 2013; Ikenouchi et al., 2005), and regulation of toll-like receptors (TLRs) and/or  
1904 IL-1R signaling (Kawagoe et al., 2008; Lin, Lo, & Wu, 2010; Muzio et al., 1997).

1905

1906 (9) *The major histocompatibility complex and maternal-fetal immune dynamics*

1907 A substantial amount of literature on maternal-fetal immune dynamics was focuses on uNK  
1908 cells. Uterine NK cells have a distinct phenotype and function from peripheral NK cells. They  
1909 have several activating receptors (Manaster & Mandelboim, 2010) but do not exert cytolytic  
1910 functions on embryonic trophoblasts that they are in contact with (King, Birkby, & Loke, 1989).  
1911 Allorecognition of embryonic placental cells by uNK cells is a key regulator of the maternal-fetal  
1912 immune mechanisms that support placentation in mammals (Moffett & Colucci, 2014). When  
1913 cells lose their ability to express any HLAs, uNK cells are shown to kill them (Hunt et al., 2005;  
1914 Ishitani et al., 2003; King, Allen et al., 2000).

1915 In humans, expression of the classical MHC class I (C-MHCI) molecule HLA-C, and  
1916 nonclassical MHC class I (NC-MHCI) molecules HLA-E, HLA-F and HLA-G on trophoblasts  
1917 inhibit uNK cell-mediated cytotoxicity (Hunt et al., 2003; King, Burrows et al., 2000). Differing  
1918 from this, mismatched HLA-C profiles trigger rejection of the transplanted organs (Petersdorf et  
1919 al., 2014). Selection for balanced polymorphisms in HLA-C alleles and their killer  
1920 immunoglobulin receptors (KIRs) is proposed to be driven by reproductive success, rather than  
1921 immune recognition of pathogens (Trowsdale & Betz, 2006). Dimorphisms of HLA-C emerged  
1922 recently within primates (Adams & Parham, 2001).

1923 Similar patterns in MHC profiles have been explored in other viviparous amniotes. C-MHCI  
1924 antigen, H2-K, is expressed on giant trophoblast cells of mice and this is attributed to  
1925 trophoblast-induced uterine vasculature transformation (Arcellana-Panlilio & Schultz, 1994;  
1926 Chatterjee-Hasrouni & Lala, 1982; Hedley et al., 1989; King et al., 1987; Sellens, Jenkinson, &  
1927 Billington, 1978). H2-D antigen is co-expressed with H2-K in virtually all their other nucleated  
1928 cells (Madeja et al., 2011). However, H2-K expressing trophoblasts lack H2-D expression. This

1929 parallels the expression patterns of C-MHC molecules at the maternal-fetal interface in humans  
1930 and may be an evolutionarily conserved pattern (Madeja et al., 2011).

1931 In humans, NC-MHCI molecule, HLA-G, is especially tolerogenic (Carosella et al., 2015;  
1932 González et al., 2012; Hviid et al., 2004; Kovats et al., 1990). In adults, HLA-G is almost  
1933 exclusively expressed by fetal trophoblasts compared to adult cells (Faulk & Temple, 1976;  
1934 King, Burrows et al., 2000; Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al.,  
1935 1997). It supports immunotolerance at the maternal-fetal interface (Rebmann et al., 2014). The  
1936 role of HLA-G in supporting tolerogenic responses to organ transplants appears to be an  
1937 exploitation of its role in immunotolerance in the utero during pregnancy (Rebmann et al., 2014).  
1938 HLA-G is upregulated by several molecules that serve essential roles during gestation including  
1939 progesterone (Yie, Xiao, & Librach, 2006; Yie et al., 2006), IFN- $\alpha$ , IFN- $\beta$ , and IFN- $\gamma$  (Rebmann  
1940 et al. 2003; Lefebvre et al., 2001; Ugurel et al., 2001; Yang, Geraghty, & Hunt, 1995), and IL-10  
1941 and TGF- $\beta$  (Cadet et al., 1995; Moreau et al., 1999).

1942 A similar NC-MHCI gene to HLA-G exists in horses (Davies et al., 2006) where it likely  
1943 functions to protect the embryo from NK-cell mediated attack (Ott et al., 2014). NC-MHC  
1944 molecules with similar structure to HLA-G are also found in Rhesus monkeys (Boyson et al.,  
1945 1997) and baboons (Stern et al. 1987). Mice have two NC-MHCI genes that are expressed on the  
1946 surface of their placentas and on pre-implanted embryos (Sipes et al., 1996).

1947 In the gestating uterus of the viviparous skink, *Pseudemoia entrecasteauxii*, four putative C-  
1948 MHCI and two putative NC-MHCI molecules are expressed (Murphy, Thompson, & Belov,  
1949 2009). This pattern resembles the C-MHCI and NC-MHCI expression profiles of mammals,  
1950 suggesting that this viviparous skink utilizes a similar physiological mechanism to 'hide' the  
1951 embryo (Murphy, Thompson, & Belov, 2009). One of the putative NC-MHCI genes (Psen-



1952 160Ut/Psen-78G) has a substitution at position 150 where a tryptophan is substituted for a  
1953 leucine (Murphy, Thompson, & Belov, 2009). When Psen-160Ut/Psen-78G was aligned to NC-  
1954 MHC I genes of vertebrates ranging from fish to eutherian mammals, tryptophan was conserved  
1955 at position 150 except in Psen-160Ut/Psen-78G and HLA-G (Murphy, Thompson, & Belov,  
1956 2009). Whether this reflects an evolutionary history associated with immune tolerance at the  
1957 maternal-fetal interface in *Pseudemoia entrecasteauxii* requires further investigation.

1958 MHC I genes are also expressed in reproductive tissues of oviparous skinks (*Ctenotus*  
1959 *taeniolatus* and *Lampropholis guichenoti*) during non-reproductive periods and during late  
1960 gravidity (Murphy, Thompson, & Belov, 2009). A similar pattern is found in viviparous skinks  
1961 *Eulamprus tympanum*, *Niveoscincus metallicus*, *Pseudemoia entrecasteauxii* and the  
1962 reproductively bimodal skink *Saiphos equalis* which all express MHC I genes at non-  
1963 reproductive periods and during late pregnancy/gravidity (Murphy, Thompson, & Belov, 2009).  
1964 MHC gene H2-EA is also expressed during gestation with long egg retention in *Saiphos equalis*.

1965 The butyrophilin subfamily 1 member A (*BTN1A1*) is located in the MHC I region of the  
1966 genome in mammals (Trowsdale, 2011). *BTN1A1* is differentially expressed in the uterus during  
1967 gestation in a viviparous lizard, *Chalcides ocellatus* (Brandley et al., 2012). *BTN1A1* may have  
1968 important antimicrobial properties in chicken eggshells (Mann, Maček, & Olsen, 2006). In  
1969 mammals *BTN1A1* is the major protein associated with fat droplets in milk (Jeong et al., 2009).

1970

1971 (10) *Microchimerism and maternal-fetal immune dynamics*

1972 Billingham, Brent and Medawar suggested the concept of actively acquired immunologic  
1973 tolerance during pregnancy 70 years ago (Billingham, Brent, & Medawar, 1953; Ribatti, 2015).  
1974 Subsequent research over the following decades revealed that substantial transfer of proteins,

1975 parasites and even immunologically active cells occurs between mother and embryo (Adams &  
1976 Nelson, 2004; Axiak-Bechtel et al., 2013; Bakkour et al., 2014; Burlingham, 2010; Fujiki et al.,  
1977 2008; Gitlin et al., 1965; Khosrotehrani et al., 2005; Owen, 1945; Turin et al., 2007).  
1978 Microchimerism, where there is <0.1% donor chimeras in host tissue, is relatively pervasive  
1979 among eutherians during pregnancy. It plays a role in establishing tolerance to non-inherited  
1980 antigens. For example, cell populations from the mother that are transferred into embryonic  
1981 lymph nodes enable the establishment of embryonic Tregs that are tolerogenic toward non-  
1982 inherited maternal antigens (Mold et al., 2008).

1983       Microchimeric cellular populations are transferred across all placental types (Axiak-Bechtel  
1984 et al., 2013; Bakkour et al., 2014; Fujiki et al., 2008; Khosrotehrani et al., 2005; Turin et al.,  
1985 2007). Fetal and maternal cells persist for decades after birth across a range of tissues in mother  
1986 and offspring, respectively (Adams & Nelson, 2004; Bakkour et al., 2014; Bayes-Genis et al.,  
1987 2005; Bianchi et al., 1996; Evans et al., 1999; Jonsson et al., 2008; Stevens et al., 2004). There is  
1988 even a call in the immunology literature to shift from the conventional paradigm of “self vs  
1989 other” to instead consider the “self” as inherently chimeric (Nelson, 2012). Given that  
1990 epitheliochorial placentation is sufficient to illicit microchimeric cell populations, the occurrence  
1991 of similar bidirectional cellular traffic is a reasonable possibility in viviparous squamates.

1992

1993       (11)       *Paternal alloantigens*

1994       Under tenants gleaned from transplant medicine, the maternal immune system would illicit  
1995 an attack response as early as insemination when maternal tissues are exposed to paternal  
1996 alloantigens (Borziak et al., 2016; Schumacher & Zenclussen, 2015; Seavey & Mosmann, 2006).  
1997 Instead, maternal cells immunologically recognize them at this time without attack (Schumacher

1998 & Zenclussen, 2015; Seavey & Mosmann, 2006; Zenclussen et al., 2010). Treg expansion, a  
1999 process with major influence on maternal-fetal immunotolerance in mammals, is proposed to be  
2000 driven by several different factors found in seminal plasma (Baratelli et al., 2005; Teles et al.,  
2001 2013). Mothers may maintain fetal-specific Tregs with memory of the paternal alloantigens  
2002 (Zenclussen et al., 2010), expediting Treg response in future pregnancies with the same father  
2003 (Rowe et al., 2012).

2004 Alloantigen exposure at the time of insemination is not restricted to mammals. Seminal fluid  
2005 of chickens contains two MHC I paternal alloantigens and one MHC II alloantigen (Borziak et  
2006 al., 2016). It also contains proteins involved in immunity and antimicrobial defenses (Borziak et  
2007 al., 2016). In hens, evidence suggests that a protective local immunity to pathogens is established  
2008 after exposure to semen but the mechanisms for this remain unclear (Reiber & Conner, 1995;  
2009 Reiber, Conner, & Bilgili, 1995).

2010 In mammals, paternal alloantigens and cytokines in seminal fluid drive immune tolerance  
2011 (Schjenken & Robertson, 2014). Mammalian seminal plasma contains immune-factors (Kelly,  
2012 1995; Schjenken & Robertson, 2014)—TGF- $\beta$  (Breuss et al., 1993; Chu & Kawinski, 1998;  
2013 Slater & Murphy, 1999), IL-8 (Gutsche et al., 2003), and soluble IL-2 receptor (Srivastava,  
2014 Lippes, & Srivastava, 1996), prostaglandin E2 (PGE2) and 19-hydroxyprostaglandin E (19-  
2015 hydroxy PGE) (Denison et al., 1999), soluble tumor necrosis factor (TNF) receptors (Liabakk et  
2016 al., 1993), receptors for the Fc portion of  $\gamma$ -globulin, spermine (Evans, Lee, & Flugelman, 1995),  
2017 and complement inhibitors (Kelly, 1995). In horses and pigs, respectively, the proteins CRISP3  
2018 (Doty et al., 2011), PSP-I and PSP-II (Rodriguez-Martinez et al., 2010), act as signaling agents  
2019 in seminal fluid.

2020 Secretions of growth factors, cytokines and chemokines from cervical and endometrial  
2021 tissues immediately following insemination generates a proinflammatory environment that likely  
2022 aids in implantation. In the utero-vaginal junction of chickens and the utero-tubal junction of  
2023 pigs, expression of several genes were shared following mating compared to non-mating and  
2024 these genes were involved with immune-modulation (*IFIT5*, *IFI16*, *MMP27*, *ADAMTS3*, *MMP3*,  
2025 *MMP12*) and pH-regulation (*SLC16A2*, *SLC4A9*, *SLC13A1*, *SLC35F1*, *ATP8B3*, *ATP13A3*), a  
2026 process essential for implantation (Atikuzzaman et al., 2017, 2015). Instead of mounting an  
2027 attack, it appears that the uterine immune system and paternal genes work cooperatively to  
2028 support pregnancy in mammals and gravidity in birds. Whether this applies to reptiles, and how  
2029 it may influence immune dynamics involved with squamate parity mode evolution, deserves  
2030 investigation.

2031

2032 (12) *Discussion and future directions—maternal-fetal immune dynamics & the*  
2033 *evolution of parity modes*

2034 Immune processes appear to be important for both oviparity and viviparity—as evidenced  
2035 here, in part, by overlapping expression profiles of immune genes in female reproductive tissues  
2036 of chickens and pigs, expression of paternal antigens in avian seminal fluid, and uterine  
2037 expression of maternal antigens in oviparous and viviparous skinks. This highlights the scientific  
2038 advances made since Medawar’s paradigm, when embryos were treated as analogs to allografts.  
2039 Nonetheless, viviparity is associated with complex immune dynamics between maternal, fetal,  
2040 and paternal tissues.

2041 Overall, evolving appropriate immunological responses is one hurdle of transitions to  
2042 viviparity in squamates. This is evidenced by the unique MHC expression profiles identified in

2043 some viviparous skinks compared to oviparous relatives (Murphy et al., 2009); and the detection  
2044 of divergent selection in immune response genes in viviparous and oviparous *Zootoca vivipara*  
2045 (Recknagel et al., 2021a). Labile parity modes in squamates may be supported if they are more  
2046 heavily reliant on the innate immune system for reproduction. However, reptiles may not have  
2047 distinguished innate and adaptive immune systems (Zimmerman et al., 2020).

2048 Changes to genes that serve overlapping functions across the Main Five may have a  
2049 disproportionate influence on transitions between parity modes. In this section I reviewed two  
2050 molecules, *TGF-β* and progesterone, that exert influence on multiple Main Five categories.  
2051 Progesterone influences uterine quiescence (embryonic retention), hepatic vitellogenesis  
2052 (nutrient provisioning) and regulation of inflammatory responses in utero (maternal-fetal  
2053 immune dynamics). Genes in the *TGF-β* family play a role in placental development and  
2054 maternal-fetal immune dynamics. *TGF-β* family is implicated in placental development in  
2055 eutherians (Hempstock et al., 2004; Caniggia et al., 2000; Lafontaine et al., 2011). A *TGF-β*  
2056 receptor protein (*TGFBR1*) was associated with placental development in *Phrynocephalus*  
2057 *vlangalii* (Gao et al., 2019). In humans *TGF-β* upregulates tolerogenic HLA-G in utero and is an  
2058 immune factor in mammalian seminal fluid. Multiple genes in the *TGF-β* family are also  
2059 differentially expressed during gestation in other viviparous lizards, *Pseudemoia entrecasteauxii*  
2060 and *Saiphos equalis* (Foster et al., 2020; Griffith et al., 2016). Examining the functions of *TGF-β*  
2061 and progesterone across other amniotes may reveal insights into how these molecules influence  
2062 the evolution of parity modes.

2063 In mammals, inflammation appears to be involved with two of the Main Five processes—  
2064 regulation of maternal-fetal immune dynamics and embryonic retention. It is intriguing to  
2065 consider the implications this has for the interconnectedness of the Main Five. Greater

2066 interconnectedness would suggest that changes to few genes involved with the Main Five could  
2067 cause a cascading effect to support more labile transitions between parity modes.

2068       Implantation and parturition in therian mammals evolved from a shared inflammatory  
2069 attachment reaction (Hansen et al., 2017). The process of implantation has important  
2070 implications for maternal-fetal exchanges of inorganic and organic material and maternal-fetal  
2071 immune dynamics. Given that inflammation is associated with implantation and parturition  
2072 implicates it in gas, water, and nutrient provisioning (including calcium here), maternal-fetal  
2073 immune dynamics and length of embryonic retention. However, implantation in mammals and  
2074 viviparous squamates is not homologous (Griffith, Van Dyke, & Thompson, 2013). Therefore, it  
2075 is difficult to make inferences about how substantial the influence of inflammation is on the  
2076 evolution of parity modes in squamates. Nonetheless, the abundant literature on uterine  
2077 inflammatory processes during human pregnancy and the evolution of inflammatory processes  
2078 that supported the evolution of viviparity in mammals (Challis et al., 2009; Chavan, Griffith, &  
2079 Wagner, 2017; Mor et al., 2011; Griffith, Chavan et al., 2017; Stadtmauer & Wagner, 2020a)  
2080 serve as indispensable resources for exploring the role of inflammation in squamate viviparity. I  
2081 resist expanding on this further. I suspect that the immune system plays a central role in dictating  
2082 the plasticity of parity modes. However, further work is necessary to validate this.

2083

2084

## 2085       **VII. Conclusions**

2086

2087       (1) Through holistic consideration of the unique complexity of parity mode evolution, within  
2088       the context of genomic and transcriptomic studies across interdisciplinary fields, this

2089 review provided a new perspective on the history of parity mode transitions in amniotes  
2090 and squamates. The overlapping activity of immune genes in utero, genes for calcium  
2091 transport, placentation, and hormonal regulation across mammals, birds, and reptiles hint  
2092 at discoveries to be made. There is a fascinating history to the evolutionary physiology  
2093 and genomics of reproduction in amniotes that is ripe for downstream research.

2094 (2) Changes to gene(s) or physiological processes associated with more than one of the Main  
2095 Five should disproportionately influence parity mode evolution—*SLC* gene superfamily,  
2096 TGF- $\beta$ , *BMPRI1B*, progesterone, *PMCA*, calbindin-D28K, *SPP1*, sustained functioning of  
2097 the corpora lutea and inflammation, and the genes associated with both gestation length  
2098 and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).

2099 (3) Growing evidence in the medical literature suggests that immune system interactions at  
2100 the maternal-fetal interface in mammals did not evolve simply through immunotolerance,  
2101 evasion, immunosuppression, or immunological barriers (Chaouat, 2016; Chavan,  
2102 Griffith, & Wagner, 2017; Moffett & Loke, 2004, 2006). Instead, maternal-fetal immune  
2103 dynamics have a deep evolutionary history that enables both embryo and mother to  
2104 interact cooperatively (Yoshizawa, 2016). Viviparity and extended embryonic retention  
2105 are assuredly associated with immunological responses across amniotes, including  
2106 squamates (e.g. Foster et al., 2020). Oviparous birds and squamates are also known to  
2107 differentially express genes during gravidity, with one exception to my knowledge,  
2108 *Lampropholis guichenoti* (Griffith et al., 2016).

2109 (4) Compared to viviparous endothermic amniotes, ectothermy likely influences parity mode  
2110 evolution differently because it entails slower antibody responses and a greater reliance  
2111 on climatic conditions for embryonic development. This and the Cold Climate

2112 Hypothesis are likely relevant to the origin of the amniotic egg and squamate parity mode  
2113 evolution. Climatic shifts during the origin of amniotes should be explored for their  
2114 consistency with the EER model.

2115 (5) Two new mechanisms for transitions between oviparity and viviparity, without  
2116 necessitating intermediate stages, stand out from the cumulative research on the Main  
2117 Five. These are presented here (Conclusions 6 and 7) as tools to be broadened and  
2118 challenged with the goal of advancing scientific insight on the subject.

2119 (6) The genomics and physiology of amniote parity mode evolution does not preclude an  
2120 origin of viviparity in the MRCA of Lepidosauria. I propose the following mechanism—a  
2121 change to the phenotype or function of mammillary knobs occurred in the MRCA of  
2122 Lepidosauria, instantaneously preventing calcium carbonate deposition (basal cap  
2123 hypothesis); the eggshell loss enabled uterine exposure to chorioallantoic progesterone  
2124 production (extending embryonic retention) and incipient calcium matrotrophy  
2125 (supporting embryonic development); parturition occurred via 1) placental progesterone  
2126 withdrawal or 2) overdistension of the uterus triggers contractions. This is one way to  
2127 imagine viviparity evolving in the MRCA of Lepidosauria.

2128 a. Hypothesis testing: If the genes that code for the KS-proteoglycan, “mammillan”,  
2129 that makes up mammillary knobs are absent or non-functional across squamates  
2130 and tuatara, then this would support the basal cap hypothesis. To test this  
2131 hypothesis, the genes must be identified in Archelosaur genomes and proteomes.  
2132 Additionally, ancestral state reconstructions on the eggshell and eggshell  
2133 membrane should be generated across oviparous and viviparous Archelosaurs,  
2134 utilizing current recommendations for characterizing eggshell microstructure



2135 (Legendre et al., 2022). This will require also developing a system to accurately  
2136 characterize eggshell membranes.

2137 (7) The calcium secreting capacity of the uterus is maintained in oviparous and viviparous  
2138 squamates. Therefore, a reversal back to oviparity may evolve through the following  
2139 sequence of events—calcium secretions in utero stick to the eggshell membrane instead  
2140 of being absorbed by the chorioallantois; oviposition can then occur early in embryonic  
2141 development in one of two ways 1) the death of corpora lutea or 2) the calcified eggshell  
2142 blocks a threshold of chorioallantoic progesterone production from reaching uterine  
2143 tissue; the calcified eggshell then provides embryonic calcium that is transported upon  
2144 embryonic metabolic demand.

2145 a. Hypothesis testing: Recent reversals should have physiological or genomic  
2146 remnants of a viviparous past. Given that viviparous squamates generally have  
2147 more active uterine immune systems to support gestation, oviparous reversals  
2148 should 1) have more immune genes expressed in utero than ancestrally oviparous  
2149 squamates, and 2) these immune genes should have stronger signatures of relaxed  
2150 selection than immune genes expressed in a close relative during viviparous  
2151 gestation.

2152 (8) Throughout this review, I highlighted the immunological problem of pregnancy by  
2153 examining evidence for Medawar's Paradigm across birds, reptiles, and mammals. In  
2154 doing so, I identified only one species that does not differentially express any genes while  
2155 the egg is in utero, *Lampropholis guichenoti* (Griffith et al., 2016). Given that an  
2156 immunological response to gravidity is evidenced in birds and multiple oviparous

2157 squamates, we can understand that *L. guichenoti* either achieves gestation through tenants  
2158 of Medawar's Paradigm or that gravidity is not an immunological problem in this species.  
2159 (9) I also demonstrated how Medawar's Paradigm is not a good explanation for viviparous or  
2160 oviparous gestation/gravidity in amniotes. Some work also suggests that viviparity in  
2161 anamniotes causes no immunological problems (Chaouat, 2016). Therefore, I  
2162 conceptualize amniotes as originating in an immunological environment that tolerated  
2163 exposure to the egg without an immunological issue. I suggest researchers utilize  
2164 *Lampropholis guichenoti* as a model for the origin of the amniote egg. If supported by  
2165 future research, then oviparous populations of *Saiphos equalis* and *Zootoca vivipara* may  
2166 represent reversals because they have substantial differential gene expression during  
2167 gravidity (Foster et al., 2020; Recknagel et al., 2021) and the oviparous population of  
2168 *Lerista bougainvillii*, which has only two differentially expressed genes during gravidity,  
2169 may represent an ancestrally oviparous state (Griffith et al., 2016). Future work can test  
2170 this by applying point 7.A in this conclusion and should measure differentially expressed  
2171 genes across stages of gravidity in *L. bougainvillii*.

2172 (10) Given that the mammillary layer is described as unique to Archelosaurs, the original  
2173 oviparous amniote eggshell may have lacked a mammillary layer. Instead, it makes  
2174 logical sense that the original oviparous amniote egg became ensheathed in an eggshell  
2175 membrane, followed by calcium deposition that looks comparable to what we see in  
2176 squamates. We can test this by using the framework of the basal cap hypothesis,  
2177 described briefly in point 6 of this conclusion and at length in section III.3.

2178  
2179

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2185       **IX.   References**

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