

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

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9 **Abstract**

10

11 There is a current lack of consensus on the ancestral parity mode, oviparity (egg-laying) and  
12 viviparity (live-birth), of amniotes and squamates (snakes and lizards). How transitions between  
13 parity modes occur at the genomic level has primary importance on how science conceptualizes  
14 the origin of amniotes, and highly variable parity modes in Squamata. Within the context of  
15 interdisciplinary literature—medical, poultry science, reproductive biology, and evolutionary  
16 biology—I review the genomics and physiology of five broad processes (Main Five) expected to  
17 change during transitions between parity modes: eggshell formation, embryonic retention,  
18 placentation, calcium transport, and maternal-fetal immune dynamics. Throughout, I offer  
19 alternative perspectives and testable hypotheses regarding proximate causes of parity mode  
20 evolution in amniotes and squamates. Should viviparity have evolved early in the history of  
21 Lepidosauria, I offer the basal cap hypothesis as a proximate explanation. The framework of this  
22 hypothesis can be extended to amniotes to infer their ancestral state. Medawar’s paradigm  
23 contextualizes embryos as analogous to allografts. However, an abundance of research across  
24 mammals, birds, and reptiles demonstrates that the maternal immune response to  
25 gestation/gravidity cannot be explained by immunosuppression, inertness, evasion, or  
26 immunological barriers. However, a rare example of a species with an apparently inert response  
27 to oviparous gravidity is *Lampropholis guichenoti*, an oviparous species that differentially  
28 expresses no genes while gravid. Overall, this review grounds itself in the historical literature  
29 while offering a modern perspective on a subject that has fascinated scientists for centuries—the  
30 origin of amniotes. Based on the cumulative evidence across the Main Five, I provide a  
31 mechanism through which squamates may reverse back to oviparity without hitting fitness

32 valleys; and make predictions on the directionality of transitions in three reproductively bimodal  
33 species. The paper ends with the inference that the first amniote egg was oviparous with  
34 extended embryonic retention. As the only species I could find that has no differentially  
35 expressed genes during gravidity compared to non-gravidity, *Lampropholis guichenoti* may  
36 serve as an appropriate model for the original amniote egg. I encourage the scientific community  
37 to utilize this manuscript as a resource in comparative genomics studies, embrace the complexity  
38 of the system, and thoughtfully consider the new framework proposed.

39 *Key Words:* parity modes, amniote origins, squamates, eggshell deposition, embryonic retention,  
40 embryonic calcium provisioning, viviparity, maternal-fetal interface, comparative evolutionary  
41 genomics, squamates

42

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100 **I. Introduction**

101

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

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

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

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



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

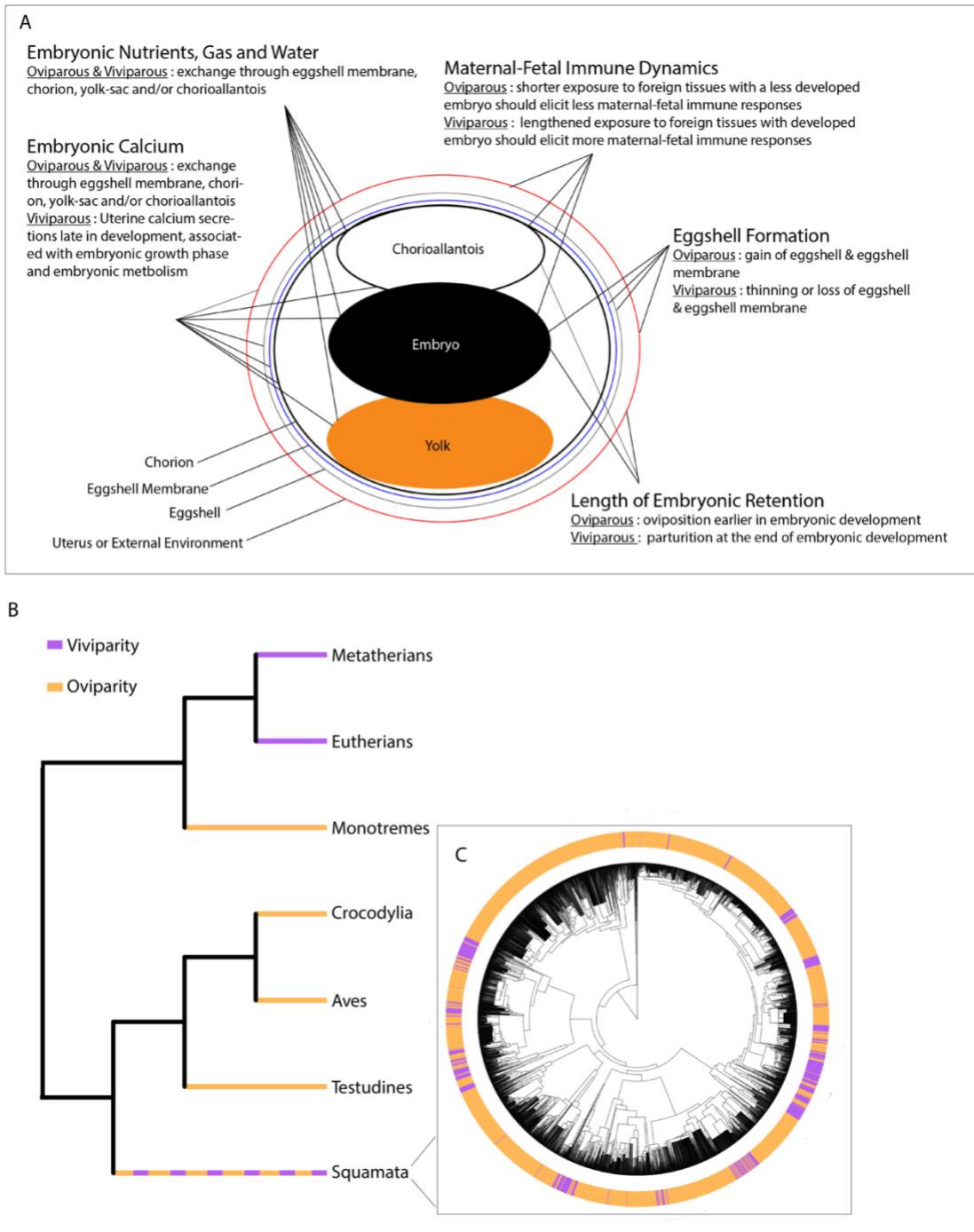
155 Discoveries of viviparity in ancient amniotes are numerous, dating back to the Early  
156 Permian (Chuliver, Scanferla & Smith, 2022; Motani et al., 2014; Piñeiro et al., 2012; Jian et al.,  
157 2023). A viviparous most recent common ancestor of amniotes is not unreasonable. Most  
158 compelling is the report that *Ikechosaurus sp.*, a basal archosauromorph, reached an articulated  
159 stage of embryonic development inside of a parchment shelled egg (Jiang et al., 2023). This  
160 brings support to the extended embryonic retention model (EER) (Hubrecht, 1910). The EER  
161 model postulates that amniote fetal membranes arose through pressure to support exposure to  
162 maternal-fetal tissues during extended embryonic retention (see Laurin et al., 2005 for a  
163 summary of earlier ancestral reconstructions of EER). It serves as an alternative to the widely  
164 accepted model that eggs laid on land prompted the evolution of fetal membranes to retain water  
165 with an eggshell that facilitated gas exchange (Romer, 1957). The discovery that hard-shelled  
166 eggs most likely evolved three times in dinosaurs, deriving from a soft-shelled ancestor (Norell  
167 et al., 2020) is consistent with the EER. As Romer (1957) phrased it “It was the egg which came  
168 ashore first; the adult followed”. This is also consistent with EER, which is compatible with both

169 oviparity and viviparity (Laurin, 2005; Mossman 1987). Throughout this review, considering  
170 viviparity as the most extreme form of extended embryonic retention, I hope to persuade readers  
171 to consider the EER model in a new light. I lay this out through a testable hypothesis on the  
172 ancestral eggshell of amniotes and Lepidosauria that can be extended to amniotes (section III.3), a  
173 phylogenetic framework to infer ancestral states based on mechanisms of maternal-embryonic  
174 calcium provisioning (section V.2), evolutionary pathways that may support transitions between  
175 parity modes (section VII.6 and VII.7), and my consensus on the parity mode of the first amniote  
176 (section VII.10).

177         Regardless of disagreements, it is sensible to equate the EER with pre-adaptations of the  
178 egg to land. Without substantial amounts of water, converting yolk nutrients to somatic tissue is  
179 impossible (Thompson & Speake, 2003). Water is the primary resource provisioned by the  
180 mother of viviparous squamates and it is stored in extraembryonic membranes (Lourdais et al.,  
181 2015). For example, water and gas exchange are associated with poor chorioallantoic blood flow  
182 (Wootton et al., 1977). In oviparous *Saiphos equalis*, a species with extended embryonic  
183 retention, the chorioallantois thickens to support embryonic growth in late development (Parker  
184 et al., 2010). Thus, if the amniote egg evolved via the EER model, it may have prompted the  
185 origin of extraembryonic membranes of amniotes. This translates to an egg washed ashore that  
186 has already evolved to withstand dryer environments.

187         Although models that restrict parity mode evolution to be unidirectional (from oviparity  
188 to viviparity) are shown to be poor fits for squamates (Pyron & Burbrink; Recknagel et al.,  
189 2021b), there is resistance to the proposition that viviparity originated early in Squamata (e.g.  
190 Griffith et al., 2015). The most recent ancestral state reconstruction, built from biomineralization  
191 and parity mode data across 80 extinct and extant amniotes using a single structured Markov

192 model, inferred viviparity with extended embryonic retention in the first amniotes and in the  
193 most recent common ancestor of Lepidosaurs (squamates and sphenodontia) (Jiang et al., 2023).  
194 However, maximum parsimony, and alternative maximum likelihood and Bayesian  
195 reconstructions did not estimate viviparity in the most recent common ancestor of Lepidosaurs  
196 (Jiang et al., 2023). A testable hypothesis regarding a molecular mechanism that may have  
197 supported a transition to viviparity at the base of squamates and extended embryonic retention at  
198 the base of amniotes will help conclude these decades long debates.



199

200 **Figure 1:** Schematic demonstrating (A) the anticipated processes that change during transitions  
 201 between oviparity and viviparity, and the organs associated with those changes. Lines from the  
 202 process to different organs indicate the organs expected to be involved with the evolutionary  
 203 shift between oviparous and viviparous phenotypes. (B) relationships between major amniote

204 clades and their associated reproductive mode, and (C) the variation of reproductive modes  
205 across squamates. The squamate phylogeny is adapted from Pyron et al., (2016) and reproductive  
206 modes of squamate species from Pyron & Burbrink (2014).

207

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

220         With a deep review of interdisciplinary literature across amniotes and associated  
221 supplementary materials, I explore genomic and physiological features of gestation and  
222 gravidity, including those that could be exploited to support labile shifts, ancestral viviparous  
223 states in amniotes and squamates, and those that may facilitate or impede reversals. I propose the  
224 framework of the basal cap hypothesis to help elucidate the ancestral parity modes of squamates  
225 and amniotes. It details how squamates may have transitioned to viviparity (an extreme form of  
226 extended embryonic retention) early in their evolutionary history. After much consideration, I

227 advocate for using squamates as a model to understand the ancestral state of the amniote egg  
228 (section VII.8 and VII.9). Future work should consider this thoughtfully and embrace the  
229 complexity of the system. I hope this manuscript serves as a foundation for further research on  
230 the evolutionary history of the amniote egg and reproductive mode evolution.

231

232 *(1) Terminology*

233 I use the conventional definition of viviparity as retention of eggs until the stage when the  
234 embryo is fully developed (Blackburn & Stewart, 2021; van Dyke et al., 2014). Oviparity is  
235 defined by eggs that develop outside the mother. I use the terms gravidity and gestation to  
236 describe the period of internal retention of the embryo in oviparous and viviparous taxa,  
237 respectively. Vertebrate placentas are conventionally defined by apposition of maternal and fetal  
238 tissues. It is accepted that all viviparous squamates have a chorioallantoic placenta under this  
239 definition (Blackburn & Stewart, 2021; Stewart & Blackburn, 1988). The avian chorioallantoic  
240 membrane and mammalian chorioallantoic placenta are homologous (Metcalf & Stock, 1993). I  
241 sometimes refer to this organ as the chorioallantoic tissue to describe it for both parity modes.  
242 Oviposition refers to the process and act of egg-laying, while parturition refers to the process and  
243 act of giving birth to live-young. Parition refers to both oviposition and parturition (Blackburn,  
244 1992; Smith, 1975).

245

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

247 Several physiological features are expected to change during transitions between  
248 oviparity and viviparity (Figure 1). I break this down into five physiological features (hereafter  
249 Main Five)—1) length of embryonic retention (Murphy & Thompson, 2011; Packard et al.,

250 1977)—only viviparous mothers retain the embryo for the entirety of development; 2) eggshell  
251 formation (Heulin et al., 2005; Packard et al., 1977; van Dyke et al., 2014)—viviparous embryos  
252 generally do not have an eggshell; 3) placental development for maternal-fetal exchange of  
253 required water, gas and/or nutrients (Blackburn, 1992, 2015; Thompson et al., 2000; Thompson  
254 & Speake, 2006); 4) embryonic calcium provisioning (Packard et al., 1985; Shadrix et al., 1994;  
255 Thompson & Speake, 2006)—sources of embryonic calcium and timing of uterine calcium  
256 secretions generally differs between oviparous and viviparous reproduction; 5) maternal-fetal  
257 immune dynamics (e.g., Graham et al., 2011; Hendrawan et al., 2017; Foster et al., 2020)—  
258 viviparous reproduction is associated with maternal and embryonic exposure to foreign tissues,  
259 which is likely to require enhanced regulation of maternal-fetal immune systems.

260

## 261 **II. Length of Embryonic Retention**

262

263 Viviparous amniotes retain the embryo until it is fully developed, but oviparous amniotes  
264 retain the embryo for a fraction of that time. Rather than using precocious hatching and  
265 parturition (PH&P), like that of opossums and early viviparous mammals (Wagner et al., 2014),  
266 squamates evolve viviparity through extended egg retention (García-Collazo et al., 2012; Shine,  
267 1983). Thus, processes affecting the length of embryonic retention are expected to change to  
268 support transitions between parity modes (van Dyke et al., 2014).

269

### 270(1) *Parturition & oviposition*

271 The genes and hormones involved with initiating and ending gestation may provide insights  
272 into the tools squamates can co-opt to change the length of embryonic retention during parity

273 mode transitions. Parturition terminates embryonic retention. Parturition can be divided into four  
274 parts (Terzidou, 2007; Vannuccini et al., 2016)—quiescence (Phase 0), activation (Phase 1),  
275 stimulation (Phase 2) and involution (Phase 3). In eutherian mammals, several processes  
276 contribute to the initiation and termination of gestation including inflammation (Challis et al.,  
277 2009; Hansen et al., 2017), maternal recognition of pregnancy (MRP), mechanical stretch of  
278 uterine tissues (Sooranna et al., 2004; Shynlova et al., 2008), and fluctuating concentrations of  
279 corticotropin-releasing hormone, progesterone, and estrogen (Challis et al., 2000; Condon et al.,  
280 2004; Shaw & Renfree, 2001).

281

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

283 Extended embryonic retention could be achieved by triggering mechanisms that extend  
284 uterine quiescence, inactivity of the uterus. Inhibition of myometrial contractions through  
285 sustained progesterone production supports quiescence across different viviparous amniotes  
286 (Bazer, 1992; Casey & MacDonald, 1997; Fergusson & Bradshaw, 1991; Ilicic et al., 2017;  
287 Murphy & Thompson, 2011; Putnam et al., 1991; Soloff et al., 2011). The corpus luteum (or  
288 plurally called corpora lutea), a transient progesterone-producing organ, produces progesterone  
289 during gestation. Extended lifespan of the corpus luteum likely aided the evolution of viviparity  
290 in mammals (Amoroso, 1968; Callard et al., 1992; Stouffer & Hennebold, 2015). Thus, early  
291 research on squamate viviparity also explored the influence of corpus luteum lifespan. The  
292 lifespan of corpora lutea associates with oviparous egg retention and oviposition (Diaz, Alonso-  
293 Gomez & Delgado, 1994; Fox & Guillette 1987; Jones & Guillette 1982). Eggshell formation in  
294 oviparous Whiptail lizards, *Cnemidophorus uniparens*, is even disrupted by experimental  
295 removal of corpora lutea (Cuellar, 1979). The lifespan of corpora lutea do not consistently



296 correlate with length of embryonic retention in viviparous squamates like it does in mammals  
297 (Albergotti & Guillette, 2011; Callard et al., 1992).

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

308 Different genes are signaled by embryos for MRP across mammals. Human chorionic  
309 gonadotropin hormone (hCG) establishes MRP (Ross, 1979; Behrman et al., 1993; Duncan,  
310 McNeilly, & Illingworth, 1998; Duncan, 2000; Ticconi et al., 2007). In pigs, MRP is  
311 hypothesized to be triggered by collaborative signaling of estradiol (E2) and prostaglandins  
312 (PGs) (Geisert et al., 2023). Similarly, glycoproteins, estradiol and prostaglandin E2 (PGE2)  
313 have been implicated in signaling MRP in horses (Klein & Troedsson, 2011; Klein, 2016). In  
314 ruminants, embryonic signaling of IFN- $\tau$  establishes MRP (Bazer, 2013; Bazer, Spencer & Ott,  
315 1997; Thatcher et al., 1995). During gestation in the uterus of viviparous African Ocellated  
316 skinks, *Chalcides ocellatus*, four receptors for interferon alpha, beta, omega, and gamma are  
317 differentially expressed but no expression of IFN- $\tau$  was detected compared to non-gestational  
318 uterine tissue (Brandley et al., 2012). I was unable to find expression patterns of MRP signaling

319 homologs in other squamate reproductive tissues. Should MRP occur in squamates, it may be  
320 signaled by genes that are clade-specific, like in mammals. This makes comparatively evaluating  
321 the influence of MRP on the evolution of viviparity an interesting avenue for future research.

322 The evolution of viviparous extended embryonic retention may be sufficiently supported by  
323 maintenance of chorioallantoic progesterone production coupled with eggshell loss (Griffith,  
324 Brandley et al., 2017). This theory may be broadly applicable across amniotes given that the  
325 most recent common ancestor of amniotes likely had a chorioallantois with an endocrine  
326 function (Griffith, Brandley et al., 2017). Following death of the corpus luteum during gestation,  
327 placental progesterone production supports extended embryonic retention in eutherian mammals  
328 (Castracane & Goldzieher, 1986; Ellinwood et al., 1989; Nakajima et al., 1991; Rothchild, 2003;  
329 Spencer & Bazer, 2004). Viviparous Italian Three-toed Skinks, *Chalcides chalcides*, shift to  
330 chorioallantoic progesterone production following degradation of corpora lutea during gestation  
331 (Guarino et al., 1998). The placenta of viviparous Southern Snow Skinks, *Carinascincus*  
332 *microlepidotus*, produces minimal progesterone but has a strong capacity to convert  
333 pregnenolone to progesterone (Girling & Jones, 2003). Whereas all genes involved with a known  
334 biosynthesis pathway for progesterone production are expressed in the placenta of horses, *Equus*  
335 *caballus*, only some of these genes were detected in the chorioallantois of chickens, *Gallus*  
336 *gallus*, viviparous Southern Grass Skinks, *Pseudemoia entrecasteauxii*, and oviparous and  
337 viviparous Southeastern Sliders, *Lerista bougainvillii* (Griffith, Brandley et al., 2017). Thus, if  
338 chorioallantoic progesterone production has supported multiple origins of viviparity in amniotes,  
339 it is not evidenced by a conserved ancestral gene expression pattern for the biosynthesis of  
340 progesterone (Griffith, Brandley et al., 2017). Nonetheless, parity trait genes in a reproductively

341 bimodal lizard, *Zootoca vivipara*, are associated with progesterone-binding functions (Recknagel  
342 et al., 2021a)—highlighting the role of progesterone in squamate reproduction.

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

361 For progesterone to prevent myometrial contractions and support quiescence, there must be  
362 progesterone receptors (PGRs) in the uterus (Mesiano et al., 2011; Young et al., 2011). In  
363 humans, progesterone responsiveness is related to specific ratios of PGRs, *PR-A* and *PR-B*, in

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

379

380 (ii) *Activation & progesterone withdrawal*

381 The activation stage of parturition is marked by the withdrawal, or functional withdrawal, of  
382 progesterone leading to an estrogen dominated response during the next state, stimulation  
383 (Bakker, Pierce, & Myers, 2017; Fergusson & Bradshaw, 1991). Progesterone may withdraw in  
384 response to environmental stimuli in reptiles during parturition (Shine & Guillette, 1988). In  
385 mammals, activation is marked by increasing concentrations of corticotropin-releasing hormone  
386 and contraction associated proteins (CAPs) including connexin-43, prostaglandins, oxytocin

387 receptors, prostanoid receptors and cell signaling proteins (Bakker et al., 2017; Ilicic et al., 2017;  
388 Leadon et al., 1982; Pashen & Allen, 1979; Whittle et al., 2000). Pro-inflammatory cytokines  
389 and chemokines, prostaglandin synthase-2 (*COX-2*, also referred to as *PTGS2*), and NF-κB also  
390 influence activation in mammals (Christiaens et al., 2008; Lappas et al., 2002; Lappas & Rice,  
391 2007; Lindström & Bennett, 2005; Olson, 2003; Terzidou, 2007).

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

401

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

403 Mechanical stretch, electrical gradients, inflammatory processes, and hormonal regulation  
404 contribute to stimulation, the phase when contractions, cervical ripening and dilation occur.  
405 Stimulation involves contributions from maternal and fetal tissues. As early as 460 BC there was  
406 uncertainty over the proportional influence of mother or fetus on the initiation of parturition.  
407 Hippocrates proposed that the fetus initiates parturition by pushing its feet on the fundus of the  
408 uterus. Although the reality is not so cartoonish, mechanical stretch of the uterus from the

409 growing embryo plays a role in parturition (Lefebvre et al., 1995; Tamizian & Arulkumaran,  
410 2004; Wray et al., 2015).

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

425 During parturition, there is an influx of uterine and embryonic pro-inflammatory genes and  
426 immune cells (Adams Waldorf et al., 2015; Charpigny et al., 2003; Mesiano et al., 2002; Park et  
427 al., 2005). Uterine contractions in humans involve actions of prostaglandins (PGs), oxytocin,  
428 corticotropin-releasing hormone, cytokines, and neutrophils (Adams Waldorf et al., 2015; De  
429 Rensis et al., 2012; Olson & Hertelendy, 1983; Park et al., 2005; Sykes et al., 2014; Terzidou,  
430 2007).

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

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

447 Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) influence, respectively, uterine  
448 contractions and cervical relaxation for partition across many amniotes including humans, *Homo*  
449 *sapiens* (Terzidou, 2007), domestic pigs (De Rensis et al. 2012), domestic chickens (Hertelendy  
450 et al., 1974; Olson et al., 1986), and Loggerhead Sea turtles (Guillette et al., 1991). Injections of  
451 PGF<sub>2α</sub> and PGE<sub>2</sub> induce parturition in viviparous Yarrow's Spiny lizards, *Sceloporus jarrovi*, and  
452 Raukawa geckos, *Woodworthia maculatus* (Cree & Guillette, 1991; Guillette et al., 1992).  
453 However, no injected dosages of PGF<sub>2α</sub> or PGE<sub>2</sub> induced oviposition in oviparous Collard

454 lizards, *Crotaphytus collaris*, Eastern Fence lizards, *Sceloporus undulatus*, Six-lined  
455 racerunners, *Aspidoscelis sexlineatus*, or Striped Plateau lizards, *Sceloporus virgatus* (Guillette et  
456 al., 1991). It is interesting that injections of  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  induced parturition in viviparous  
457 lizards but did not induce oviposition in oviparous lizards studied. Given this, it is plausible that  
458 regulatory or functional changes to  $\text{PGF}_{2\alpha}$  and/or  $\text{PGE}_2$  in squamates could facilitate changes to  
459 the length of embryonic retention to support transitions between reproductive modes. However,  
460 induction of parturition with  $\text{PGF}_{2\alpha}$  in viviparous *Woodworthia maculatus* only worked with  
461 pre-treatment of  $\beta$ -adrenoceptor (Cree & Guillette, 1991).

462  $\text{PGF}_{2\alpha}$  decreases progesterone concentrations during stimulation (De Rensis et al., 2012). In  
463 humans, biosynthesis of PGs is driven largely by the enzyme cyclooxygenase (*COX*)-2 rather  
464 than *COX-1* (i.e., prostaglandin synthase-2 and -1) (Slater et al., 1995, 1999). This helps  
465 maintain the decreased progesterone/estrogen ratio of stimulation. In ovariectomized viviparous  
466 Garter snakes, *Thamnophis*, increased estrogen stimulated thickness of uterine epithelial cells  
467 and glandular activity, whereas administration of progesterone had little influence on uterine  
468 histology (Mead et al., 1981). Uterine pig models revealed that estrogen stimulates involuntary  
469 contraction and relaxation (peristalsis) of the uterus (Mueller et al., 2006).

470 The softening of the cervix is important during the stimulation stage of parturition. A  
471 hormone related to insulin, *relaxin*, promotes myometrial softening in humans, *Homo sapiens*,  
472 domestic pigs, and turtles (Mercado-Simmen et al., 1982; Sorbera et al., 1988; Weiss &  
473 Goldsmith, 2001). The cervix also gets softer by actions of  $\text{PGE}_2$ .  $\text{PGE}_2$  activates pro-  
474 inflammatory cytokines, interleukin (IL)-8 and tumor necrosis factor (TNF)- $\alpha$ , which activates  
475 the collagenases and matrix metalloproteinases for cervical softening (Bakker et al., 2017). This  
476 causes a positive feedback loop between IL-8 and  $\text{PGE}_2$  synthesis (Denison et al., 1998;



477 Denison, Calder & Kelly, 1999; Terzidou, 2007; Li et al., 2010). Upregulated of IL-8 is also  
478 promoted by the protein complex NF-kB during parturition in humans (Elliott, 2001). Similar  
479 patterns were observed during parturition in mice and baboons (Mendelson & Condon, 2005;  
480 Mendelson, 2009).

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

493 Altered expression or phenotype of contractility agonists, oxytocin receptors and estrogen  
494 receptors, and contractility antagonists, progesterone receptors and  $\beta$ -adrenergic receptors  
495 (Ravanos et al., 2015) may also change the length of embryonic retention to support transitions  
496 between parity modes. Differences in length of embryonic retention in oviparous and viviparous  
497 agamas, *Phrynocephalus przewalskii* and *Phrynocephalus vlangalii*, appears to be driven by  
498 regulatory differences of prostaglandins, *COX-2*, an AVT receptor (*MTR*),  $\beta$ -adrenergic receptors,  
499 and estrogen receptors. During oviposition, *P. przewalskii*, exhibited the following: promotion of

500 contractions through downregulation of  $\beta$ -adrenergic receptor (*ADRB2*), and upregulation of  
501 *COX-2* and prostaglandin, and absent (potentially lost) expression of two estrogen receptors  
502 (*ESR1* and *ESR2*) and the AVT receptor, *MTR* (Gao et al., 2019). During the stage of gestation  
503 corresponding to oviposition, viviparous sister-species, *P. vlangalii*, exhibited the following  
504 alternate pattern: inhibition of contractions caused by upregulation of *ADRB2* and  
505 downregulation of two estrogen receptors (*ESR1*, *ESR2*), *MTR*, *COX-2*, and prostaglandin (Gao  
506 et al., 2019). Some viviparous squamates, *Saiphos equalis*, *Chalcides ocellatus*, and *Pseudemoia*  
507 *entrecasteauxii*, share some of these expression patterns (*COX-2*, *MTR*, and *ADRB*, respectively)  
508 thought to be involved with extended embryonic retention in viviparous *P. vlangalii* (Brandley et  
509 al., 2012; Foster et al., 2020; Gao et al., 2019; Griffith et al., 2016); and *ADRB2* is upregulated at  
510 mid-gestation in viviparous *Zootoca vivipara* compared to oviparous counterpart (Recknagel et  
511 al., 2021a). Overexpressed genes in viviparous uterine tissues of *Zootoca vivipara* also  
512 functionally enriched pathways for beta 1 and beta 2 adrenergic receptor signaling pathways  
513 (Recknagel et al., 2021a). This study, which compared uterine expression profiles during  
514 gestation across viviparous species of squamates, rodents, canines, ungulates, and humans,  
515 concluded that shared regulatory networks are recruited to support viviparity (Reckangel et al.,  
516 2021a).

517       Recently, in humans, the only Classical Major Histocompatibility Antigen (C-MHC)  
518 expressed by trophoblasts (specialized placental cells) was associated with parturition when it  
519 was discovered that HLA-C is significantly increased during laboring term and preterm placentas  
520 compared to non-laboring placentas (Hackmon et al., 2017). The authors suggested a mechanism  
521 where fetal HLA-C open conformers on the placenta provoke inflammation of maternal tissues,  
522 leading to parturition (Hackmon et al., 2017). Expression of MHC alloantigens, foreign antigens

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

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

538

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

540 The physiology of avian oviposition is dependent on a circadian schedule (Williams, 2012).  
541 A general model of an “open period”, when eggs are laid are separated by “laying gaps”  
542 (Williams, 2012). Chicken ovulation and oviposition cycles leave an 8-hour open period where  
543 luteinizing hormone (LH) and progesterone surge, initiating ovulation and continuing the cycle.  
544 At the extreme, the ancient murrelet, *Synthliboramphus antiquus*, oviposits a two-egg clutch on  
545 seven-day intervals (Williams, 2012). Longer laying intervals have been associated with longer

546 intervals between initiation of yolk development (Astheimer & Grau, 1990). Differing from  
547 birds, oviparous squamates retain eggs longer than the ovarian cycle (Tinkle & Gibbons, 1977).  
548 This suggests that oviparous squamates may rely on different molecular mechanisms to support  
549 oviposition than birds.

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

560

### 561(3) *Pre-term birth & embryonic retention mechanisms*

562 The literature on pre-term birth may be a fruitful avenue of research to inform understanding  
563 on the evolutionary genomics of embryonic retention length. Slower increases of CRH (Ellis et  
564 al., 2002) and higher expression of Neurokinin B, for example, are associated with pre-term birth  
565 in humans (Torricelli et al., 2007). Injections of RU486, a progesterone receptor (PGR)  
566 antagonist, promoted pre-term labor in rhesus macaques but the progression of physiological  
567 activity differed from normal parturition (Haluska et al., 1987). Examining homologs of genes  
568 involved with human pre-term birth in squamates may provide further candidates for genes that

569 could impact the length of embryonic retention in squamates. Some evolutionary studies are  
570 taking implications of pre-term birth into account. For example, a comparative evolutionary  
571 transcriptomics study across therians, monotremes, squamates, and an amphibian recently  
572 associated *HAND2* with preterm birth in Eutherian mammals (Marinić et al., 2021).

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

580

#### 581(4) *Discussion & future directions—embryonic retention and parity mode evolution*

582 The physiological processes involved with the start of gestation (maternal recognition of  
583 pregnancy) and the end of gestation (partition) in birds and mammals provide insights into the  
584 genes and hormones squamates may co-opt to alter length of embryonic retention during  
585 transitions between parity modes. Unsurprisingly, hormones like estrogen and progesterone, play  
586 important roles in partition across amniotes. Further processes to be examined in squamates  
587 include signaling of homologous genes for MRP, placental progesterone production, novel  
588 pathways for biosynthesis of progesterone, the role of beta 1 and beta 2 adrenergic receptor  
589 signaling pathways, fluctuating ratios of progesterone receptors, the lifespan of the corpus  
590 luteum across a broader range of taxa, production and circulation of homologs for AVT and  
591 CRH or other similarly structured genes, expression of fetal alloantigens and inflammatory

592 cytokines in utero, and the influence of uterine overdistention on contractions. Regarding  
593 squamate parity mode transitions, the role of uterine overdistention in mammalian parturition  
594 suggests a lack of uterine overdistention may be one hurdle for reversals back to oviparity.  
595 Understanding the evolutionary physiology and genomics of embryonic retention in oviparous  
596 and viviparous squamates will benefit from focused attention on reproductively bimodal species  
597 (Whittington et al., 2022) and from genomics/physiological research across more taxa that vary  
598 in reproductive modes.

599

### 600 **III. Eggshell Formation**

601

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

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

613 Monotremata (egg-laying mammals) have an eggshell but far less has been documented about its  
614 structure compared to other amniotes (Legendre et al., 2022). The structure and physiological

615 mechanisms involved with eggshell calcification are most well resolved in birds (Choi et al.,  
616 2018; Francesch et al., 1997; Jonchère et al., 2010, 2012; Rose-Martel, Du, & Hincke, 2012).  
617 Eggshell deposition in tuatara and squamates differs dramatically (Choi et al., 2018). Viviparous  
618 squamates lack an eggshell, absorb the eggshell during gestation, or have a thin layer of calcium  
619 deposits.

620 The earliest records of amniote eggshells have features characteristics of Archelosaur  
621 eggshells, including the mammillary layer (Stein et al., 2019; Legendre et al., 2022). Recent  
622 reconstructions are consistent with a thin eggshell in ancestral dinosaurs (Norell et al., 2020;  
623 Stein et al., 2019). It is important to consider that the semi-rigid shells of Lepidosaur and  
624 testudines are not homologous (Legendre et al., 2022); the microstructure of Archelosauria  
625 (birds, crocodiles, turtles and dinosaurs) and Lepidosaur eggshells are remarkably different (Choi  
626 et al., 2018); and recent reconstructions of the composition and ultrastructure of dinosaur  
627 eggshells revealed that calcified hard eggshell of dinosaurs originated three times (Norell et al.,  
628 2020). In the remainder of this section, I consider how structural, mineral,  
629 genomic/transcriptomic, and proteomic information on amniote eggshells can inform scientific  
630 understanding of the ancestral eggshell of amniotes and Lepidosaur.

631 The genetic drivers of eggshell formation are not resolved in squamates. Two oviparous  
632 lizards, *Lerista bougainvillii* and *Lampropholis guichenoti*, differentially express either zero or  
633 two genes, respectively, in utero in non-gravid vs gravid comparisons (Griffith et al., 2016).  
634 However, this study only measured gene expression at one developmental stage, making it  
635 difficult to infer if regulatory changes influence eggshell formation. Nonetheless, oviparous  
636 *Saiphos equalis* and *Phrynocephalus przewalskii* have extensive differential expression during  
637 gravidity (Foster et al., 2020; Gao et al 2019). It is interesting to see drastically different uterine

638 gene expression profiles associated with oviparity, given that shared genes are recruited to the  
639 uterus to support viviparity across diverse amniotes (Recknagel et al., 2021a). Under the  
640 assumption that conserved traits should be accompanied with more similar gene expression  
641 profiles than convergent traits, uterine gene expression profiles in themselves currently reveal  
642 more conserved regulatory networks in utero for squamate viviparity than oviparity.

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

652

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

654       The different mineral compositions of eggshells across amniotes may provide insight into the  
655 differing physiological conditions and evolutionary histories under which they are formed (Table  
656 1). Taxa use a polymorph of calcium carbonate—calcite, aragonite or vaterite—to develop the  
657 eggshell (Hincke et al., 2012). Amorphous calcium carbonate (ACC) is a transient non-  
658 crystalline precursor phase of calcite and aragonite that is important for many calcification  
659 processes in invertebrates (Hincke et al., 2012). It was recently shown to control avian eggshell  
660 mineralization (Rodríguez-Navarro et al., 2015).



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

669 There are differing accounts on the microstructure of monotreme eggshells, however  
 670 conceptus coats include three layers including zona pellucida, mocooid coat and shell coat  
 671 (Frankenberg & Renfree, 2018). Further studies are needed test for secondary homology.  
 672 Monotreme shells are described as proteinaceous, permeable, and flexible (Hughes, 1984).  
 673 Marsupials lack an eggshell but have an eggshell coat, similar to that of monotremes  
 674 (Frankenberg & Renfree, 2018), that is secreted by the epithelial cells and endometrial glands  
 675 early on in embryonic development prior to implantation (Roberts et al., 1994; Roberts & Breed,  
 676 1996). Upon hatching of the shell coat and attachment of the embryo, a cooperative  
 677 inflammatory response ensues (Stadtmauer et al., 2020a, 2020b).

678 **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

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

681

682

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

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

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

702 Reduced number or size of eggshell glands leads to reduced eggshell membrane thickness in  
703 viviparous squamates. In chickens, variation in size, spacing, and neutron density of eggshell  
704 glands may also be important for eggshell structure (Guillette & Jones, 1985). In the

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

725 In the oviparous Przewalski's toadhead agama lizard, *Phrynocephalus przewalskii*, 148 genes  
726 are highly expressed in the uterus during the stage of eggshell gland development (Gao et al.,  
727 2019). Only three of these are highly expressed in *P. vlangalii*, a viviparous close relative at this

728 time, suggesting differences in oviparous and viviparous eggshell gland development requires  
729 regulatory changes to dozens of genes (Gao et al., 2019). In the opossum, a marsupial,  
730 proliferation of uterine glands is not induced by the conceptus (Griffith et al., 2019).

731

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

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

744 Eggshell formation begins with the eggshell membrane. Two unciliated cell types in the  
745 uterus contribute to eggshell membrane formation in a viviparous skink, *Chalcides ocellatus*  
746 *tiligugu* (Corso et al., 2000). One secretes sulfated glycosaminoglycans to form the inner shell  
747 membrane, and the other which secretes acidic glycoproteins to form the outer layers (Corso et  
748 al., 2000). Simple alveolar glands in the lamina propria secrete collagen fibers (Corso et al.,  
749 2000). Inhibition of fiber formation or cross-linking, typically caused by aminopropionitrile or a

750 copper deficiency, causes distorted formations of the eggshell membrane in birds (Arias et al.,  
751 1997; Chowdhury & Davis, 1995; Hincke et al., 2012).

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

771 Parsimony would suggest that all oviparous amniotes shared an ancestral process of  
772 eggshell formation. In Archelosaurs, the process of eggshell formation relies on mammillary

773 knobs and upward growth of calcite, as described above. In Lepidosaur eggshells, which have  
774 substantially less calcite growth, calcium is deposited on the surface of the eggshell membrane  
775 and, in the case of gekkonids and the tuatara, crystal growth proceeds inward toward the center  
776 (Choi et al., 2018). The strikingly divergent structure and directionality of eggshell formation  
777 between Archelosauria and Lepidosauria suggests that the dissimilar processes of eggshell  
778 formation are a result of genetic drift (e.g. Schiffman & Ralph, 2022), selection for specific  
779 eggshell traits, or, in the case of an early origin of viviparity in Amniotes (Jiang et al., 2023)  
780 and/or Lepidosauria (Pyron & Burbrink, 2014), eggshells are a derived convergent trait.

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

796 result in a rapid loss of the eggshell and thus a relatively fast transition to viviparity or extended  
797 embryonic retention.

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

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

812 Several pieces of biological evidence lend themselves to an early origin of viviparity in  
813 Lepidosaurians and the basal cap hypothesis including—the lack of homology between the semi-  
814 rigid shells of testudines and Lepidosaurians (Legendre et al., 2022), the later stage of embryonic  
815 development when eggs are commonly oviposited in squamates (Blackburn, 1995), and the more  
816 predominant reliance on yolk calcium rather than eggshell calcium in squamates compared to  
817 Archelosaurs (Packard, 1994; Stewart & Ecy 2010). Viviparity in the most recent common  
818 ancestor of Lepidosaurians may provide clear evolutionary insights on these phenomena.

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

830 Over 500 proteins are found in the chicken eggshell matrix (Mann, Maček, & Olsen, 2006;  
831 Mikšík et al., 2007, 2010). Ovocleidin-116 (*OC-116*), ovocalyxin-36 (*OCX-36* or *BPIFB4*),  
832 ovocalyxin-21 (*OCX-21*), and ovocleidin-17 (*OC-17*) are important for avian eggshell formation  
833 (Hernández-Hernández, Gomez-Morales et al., 2008; Jonchère et al., 2010; Tian et al., 2010).  
834 *OC-116*, *OC-36*, *OCX-21*, and *OC-17* are some of the most differentially expressed genes during  
835 eggshell calcification in chickens (Gautron et al., 2007; Hincke et al., 1999, 2012; Jonchère et al.,  
836 2010). Ovocalyxin-21 may serve as a chaperone protein along with the protein endoplasmin  
837 (ENPL) to facilitate proper folding of the avian eggshell matrix (Jonchère et al., 2010). In birds,  
838 *OC-17* is concentrated in the inner mammillary cone layer, it interacts strongly with ACC, and it  
839 is implicated in early stages of biomineralization of the eggshell (Gautron et al., 2021).

840 Originally considered avian-specific, several homologs of avian eggshell matrix proteins  
841 have now been identified in non-avian reptiles and mammals (Le Roy et al., 2021). A recent



842 study found a significantly reduced number of intact avian eggshell matrix proteins in viviparous  
843 squamates compared to oviparous squamates, a pattern that was especially apparent in snakes  
844 (Xie et al., 2022). This study also found that *OC-17* was only absent in viviparous squamates but  
845 was always present in the oviparous species in the dataset (Xie et al., 2022). Due to this, and the  
846 central role of *OC-17* in avian eggshell formation in birds, they ascribe losing intact *OC17* with  
847 the prevention of reversals back to oviparity (Xie et al., 2022). However, given that *OC-17* is  
848 implicated in initiation of mineralization in the mammillary cone layer, which is absent in  
849 squamates, the necessity of *OC-17* for squamates eggshell formation requires further  
850 investigation. Other genes, like osteopontin (*OPN* or *SPPI*), also play a central role in  
851 biomineralization of the avian eggshell and should be investigated in squamates.

852 *OCX-36* and other bactericidal/permeability-increasing (BPI) family B proteins (also called  
853 *LPLUNCs*) are now thought to have a common origin in vertebrates with multiple duplication  
854 events (Gautron et al., 2007; Tian et al., 2010). Orthologs of *OCX-36* are found in Archelosauria  
855 and Monotremata (Le Roy et al., 2021). In birds, *OCX-36* plays a role in innate immune  
856 responses and is found in high concentrations in the inner eggshell membrane (Gautron et al.,  
857 2007, 2011; Tian et al., 2010).

858 *OC-116* is homologous to mammalian *MEPE*, which plays a role in bone and teeth  
859 mineralization (Bardet et al., 2010a, 2010b). In birds, *OC-116* influences shell thickness, elastic  
860 modulus, and egg shape (Le Roy et al., 2021). *OC-116* was identified in a crocodile, *Crocodylus*  
861 *siamensis*, proteome (Le Roy et al., 2021; Mikšík et al., 2018). Synteny analysis across seven  
862 turtle species and platypus (*Ornithorhynchus anatinus*) revealed absence of *MEPE/OC116* (Le  
863 Roy et al., 2021). Other genes and lncRNAs are purported to be important for the quality of  
864 eggshell formation in hens—*FGF14*, *COL25A1*, *GPX8*, and several members of the solute

865 carrier protein (*SLC*) gene family (Yang et al., 2020). Research into lncRNAs activity in  
866 squamate reproductive tissues during embryonic development represents another valuable track  
867 for research.

868 Various evolutionary genomics studies have revealed squamate-specific candidates for shell  
869 formation (e.g. Recknagel et al., 2021a; Gao et al., 2020). Some of these candidates span the  
870 major clades of amniotes. Seven of the genes expressed during eggshell gland development in  
871 *Phrynocephalus przewalskii*—*HYPOUI*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*, *RRBP1* and  
872 *TRAMI*—are purported to be important for eggshell calcification in chickens (Brionne et al.,  
873 2014). Given this overlap across species that diverged over 300 million years ago (Shen et al.,  
874 2011), these are excellent candidates for further exploration.

875 A functional genomics study harnessed hybridizations of oviparous and viviparous  
876 individuals of *Zootoca vivipara* to reveal 17 SNPs and 38 genes associated with eggshell traits  
877 (Recknagel et al., 2021a). These genes enriched terms related to cell communication and the  
878 immune system, while differentially expressed gene during gravidity enriched pathways for  
879 transforming growth factor (Recknagel et al., 2021a). The three loci with the strongest  
880 association with eggshell traits mapped closely to *LG MN*, *LYPLA1*, and *CRTCI* (Recknagel et  
881 al., 2021a). The association of these genes with eggshell traits is particularly interesting. *LG MN*,  
882 for example, is involved with the cadherin pathway. Cadherins have an established role in  
883 squamate reproduction. In squamates, previous literature discusses how cadherins influence  
884 embryonic attachment in viviparous taxa (Wu et al., 2011). *LG MN* is also differentially  
885 expressed across many viviparous squamates and mammals (Recknagel et al., 2021a). Thus,  
886 *LG MN*, appears to support both oviparous and viviparous gestation in different ways. There are a  
887 number of ways to approach exploring how *LG MN* may support both maternal-fetal

888 interconnectivity (viviparous individuals) and eggshell formation (oviparous individuals). Cell-  
889 to-cell communication analysis using single cell data on uteruses of a reproductively bimodal  
890 species would enable researchers to identify different interaction networks of *LGMN* and  
891 associated cells in oviparous vs viviparous individuals.

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

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

909

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

911 Substantial pleiotropy of genes involved with eggshell formation would imply that regardless  
912 of parity mode, taxa have innately conserved toolkits that can be readily exploited to form an  
913 eggshell for oviparous gestation. In addition to the candidate genes associated with both  
914 gestation length and eggshell traits in *Zootoca vivipara* (Reckagel et al., 2021a), several genes  
915 associated with eggshell deposition have pleiotropic effects within species or have different  
916 effects in oviparous vs. viviparous amniotes. Osteopontin (*SPP1* or *OPN*) is found in bone and  
917 kidneys, and transports calcium to other tissues in the body (Pines et al., 1995). It plays an  
918 important role in calcium carbonate biomineralization of the avian eggshell (Gautron et al.,  
919 2021). It is highly expressed in the chicken uterus during calcification (Jonchère et al., 2010) but  
920 supports pregnancy recognition and implantation in sheep (Bazer et al., 2011). Improper  
921 functioning of *SPP1* in the uterus leads to cracked and abnormal shells in birds (Arazi et al.,  
922 2009; Hincke et al., 2008).

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

931 *BMPER* and seven *BMPs* are expressed during gestation in *Chalcides ocellatus*, a viviparous  
932 skink (Brandley et al., 2012). Most of these are upregulated (Brandley et al. 2012). *BMP* genes  
933 are expressed during both gravidity and non-gravidity in oviparous *Lerista bougainvillii* and

934 *Lampropholis guichenoti* (Griffith et al., 2016). *BMP2* is upregulated in oviparous late gestation  
935 compared to viviparous late gestation in the reproductively bimodal lizard, *Saiphos equalis*  
936 (Foster et al., 2020).

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

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

954 *SLIT* genes are purported to be involved with folding the eggshell matrix in chickens  
955 (Jonchère et al., 2010). The *SLIT2* gene functions across birds and mammals in diverse organs,  
956 and encodes a protein that provides a structural framework for protein-protein interactions

957 (Jonchère et al., 2010; Marillat et al., 2002). In a functional genomics study, *SLIT2* was  
958 identified as an important gene for eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).  
959 *SLIT2* is among the 50 most downregulated genes in the uterus during pregnancy in the  
960 viviparous African ocellated skink, *Chalcides ocellatus*, compared to non-pregnancy (Brandley  
961 et al., 2012). However, in the uterus of the yolk-sac placenta in the viviparous skink, *Pseudemoia*  
962 *entrecasteauxii*, *SLIT2* is upregulated compared to non-reproductive uterine tissue (Griffith et al.,  
963 2016). *SLIT3* is differentially expressed during the stage of placentation in the viviparous agama  
964 lizard, *Phrynocephalus vlangalii* (Gao et al., 2019). *SLIT* genes also play a role in axonal  
965 pathfinding and neuronal migration in rats (Marillat et al., 2002). *SLIT2* was associated with  
966 reproduction in humans (Chen, Chu et al., 2015).

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

976

#### 977 (5) Eggshell formation termination

978 When eggshell formation is terminated, the egg is still bathed in the supersaturated  
979 calcium and bicarbonate ion fluid (Hincke et al., 2012). Some component(s) of the terminal

980 uterine fluid may prevent precipitation of calcium carbonate (Gautron, Hincke & Nys, 1997),  
981 such as phosphate anions (Lin & Singer, 2005). The presence of phosphorous in the superficial  
982 layers of the chicken shell suggest it may be a factor preventing the deposition of calcite crystals  
983 in the terminal stage. Additionally, the high concentration of *OCX-32* in the outer eggshell and  
984 cuticle, suggest that the gene may inhibit proteinaceous crystal growth in the terminal stage of  
985 eggshell calcification (Gautron, Hincke, Mann et al., 2001). It is informative to viviparous  
986 reproduction and consistent with the basal cap hypothesis that exposure to precursors of the  
987 eggshell does not necessitate eggshell deposition. The influence of phosphate anions and *OCX-*  
988 *32* on inhibition of calcium carbonate precipitation on the eggshell membrane of viviparous  
989 squamate embryos has not been examined to my knowledge.

990

#### 991 *(6) Rotating the egg for eggshell formation*

992 Oviparous amniotes rotate the egg for calcium formation and viviparous mammals rotate the  
993 embryos for parturition. One hurdle to reversing back to oviparity may be re-evolving rotation of  
994 the egg for shell formation early in gravidity (Griffith et al., 2015). Given the complex  
995 musculature of the uterus across taxa, that allows for multidirectional force for parturition and  
996 eggshell formation, it is difficult to determine the degree of difficulty for re-evolving appropriate  
997 timing of egg-rotation. Cadherins and hormonal signaling support embryonic attachment (Wu et  
998 al., 2011; Biazik et al., 2012), which can prevent rotation of the egg. Oviparous taxa lack  
999 embryonic attachment, enabling the uterus to rotate the egg for eggshell formation. This rotation  
1000 does not happen until later in gestation for eutherian mammals when, for example, the embryo  
1001 detaches and cadherins become less concentrated (Wu et al., 2011). Perhaps a candidate gene for  
1002 studying this is, a cadherin *CDH5*, the only gene that is differentially expressed in all viviparous

1003 squamates studied thus far studied (Recknagel et al., 2021a). Genes that enrich the GO term for  
1004 “voltage-gated calcium channel activity” are also useful candidates for investigating uterine  
1005 rotation associated with eggshell formation because voltage-gated calcium channels effect the  
1006 action potential of cells and can cause muscle contractions.

1007

1008 (7) *Discussion & future directions—eggshell formation and parity mode evolution*

1009 The process of eggshell formation is more resolved in birds compared to non-avian reptiles  
1010 and monotremes (Choi et al., 2018; Frankenberg & Renfree 2018). I described some overlaps  
1011 gleaned from the literature which prove as curious candidates for further research  
1012 (Supplementary Table 1). Of particular interest are avian eggshell matrix proteins (Alföldi et al.,  
1013 2011; Le Roy et al., 2021; Tian et al., 2010; Xie et al., 2022), genes with biomineralizations  
1014 functions, candidate genes associated with eggshell traits in *Zootoca vivipara* (Recknagel et al.,  
1015 2021a), and the homologs for avian eggshell matrix proteins identified in the *Anolis carolinensis*  
1016 genome (Alföldi et al., 2011; Tian et al., 2010). Additionally, genes purported to be important for  
1017 eggshell calcification in chickens associated with eggshell gland formation in an oviparous  
1018 lizard, *Phrynocephalus przewalskii*, are relevant—*HYPOUI*, *KCNMA1*, *P4HB*, *PRDX4*, *PTN*,  
1019 *RRBPI* and *TRAMI* (Brionne et al., 2014; Gao et al., 2019). Overlaps between the genes  
1020 associated with gestation length and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a)  
1021 hint at genes that could potentially evolve to innately effect multiple traits relevant to parity  
1022 mode transitions. The basal cap hypothesis also offers a simple evolutionary mechanism to  
1023 investigate the evolutionary history of amniote parity mode evolution (see section III.3).  
1024 Alternatives to the basal cap hypothesis are that dissimilar eggshells and eggshell deposition



1025 processes evolved through selective pressure, genetic drift, or both. Fortunately, the basal cap  
1026 hypothesis can be utilized to ascertain the likelihood of this.

1027

#### 1028 **IV. Placentation & Transport of Embryonic Water, Gas, and Nutrients**

1029

1030 The evolutionary pressures on fluid allocation, gas exchange and nutrient transport should  
1031 differ between oviparous and viviparous taxa because their sources of all or some of these  
1032 resources differ (Blackburn, 1992; Bonnet et al., 2001; Bonnet, Naulleau & Shine, 2017; van  
1033 Dyke et al., 2014). In viviparity, maternal gas and water are accessed through the chorioallantois,  
1034 which is especially important in the latter half of development (van Dyke et al., 2014; Carter,  
1035 2012). Nutrients can be available from the yolk, maternal transfer, or both yolk and maternal  
1036 transfer.

1037 While viviparity is associated with shared patterns of uterine gene expression during amniote  
1038 gestation (Recknagel et al., 2021a), the same does not occur in viviparous amniote placentas  
1039 (Foster et al., 2022). Instead, different genes that serve similar functions are recruited to the  
1040 placenta across independent origins of viviparity (Foster et al., 2022). Additionally, where other  
1041 amniotes can rely on the albumen for fluid allocation, squamates lack an albumen (Blackburn &  
1042 Stewart, 2021). The eggshells of various squamates supports uptake of water from the  
1043 environment (Blackburn & Stewart, 2021). The evolutionary implications of this have not been  
1044 documented to my knowledge.

1045

1046 *(1) Anatomy & methods of water, gas & nutrient provisioning*

1047       The embryonic membranes regulate embryonic fluid transport, nutrient supply, respiration,  
1048 immunity, and waste (Brace, 1997; Burton & Tullett, 1985; Ferner & Mess, 2011; Packard &  
1049 Packard, 1980). Fluids are important for the developing embryo because they prevent desiccation  
1050 and compression (Ferner & Mess, 2011; Packard & Packard, 1980). Over-abundance or under  
1051 abundance of embryonic sac fluids leads to reproductive failure (Chamberlain et al., 1984;  
1052 Fedakâr et al., 2016; Hadi, Hodson & Strickland, 1994; Mercer et al., 1984). Water is the  
1053 predominant resource provisioned from the mother in most viviparous squamates (Lourdais et  
1054 al., 2015).

1055       Oxygen flux in embryonic mammals is largely determined by oxygen-diffusing capacity of  
1056 the placenta, the rates of blood flow in the umbilical and uterine arteries, and the oxygen  
1057 capacities and affinities of fetal and maternal blood (Carter, 2009). Reptilian and mammalian  
1058 blood vessels differ in basic characteristics such as capillary density, capillary surface, and  
1059 oxygen diffusion gradients (Pough, 1980). Oviparous taxa regulate gas exchange through pores  
1060 in their eggshells.

1061       Patterns of embryonic nutrient exchange can be broadly categorized into lecithotrophy,  
1062 obtaining nutrients from the yolk, and placentrophy or matrotrophy, obtaining nutrients from the  
1063 mother. Taxa belonging to Archelosauridae are lecithotrophic. The ancestral state of mammals  
1064 was most likely oviparous matrotrophy that later evolved into viviparous matrotrophy in therians  
1065 (Blackburn, 2005). The ancestral state of reptiles was likely lecithotrophy (Blackburn, 2005).  
1066 Most viviparous squamates are lecithotrophic, some are lecithotrophic and matrotrophic, and a  
1067 few have specializations for substantial matrotrophy (e.g. Blackburn, 2015a, Blackburn, 1985b;  
1068 Stewart & Thompson, 1993; Thompson, Stewart et al., 1999; van Dyke et al., 2014). Even in  
1069 lecithotrophic viviparous squamates some degree of organic or inorganic nutrients pass through

1070 the chorioallantoic placenta (Blackburn, 2005; Swain & Jones, 1997, 2000; Stewart & Eday,  
1071 2010; Thompson, Stewart et al., 1999; Thompson & Speake, 2002). Reversals may be most  
1072 unlikely in lineages that have specialized placentas for substantial nutrient exchange because  
1073 they would need to re-evolve lecithotrophy. Highly matrotrophic squamates are extremely rare  
1074 (Blackburn, 2015a).

1075

1076 *(2) Evolutionary history of yolk-sac formation and yolk processing*

1077 Vitellogenesis is the process of yolk formation in the oocyte, providing the embryo with a  
1078 valuable source of nutrients, primarily through the accumulation of precursor proteins to yolk,  
1079 vitellogenins. Vitellogenin is produced in the liver, called hepatic vitellogenesis, and transported  
1080 to the maturing ovum (Ho, 1987). Vitellogenins were lost in all mammals except monotremes  
1081 (Brawand, Wahli & Kaessmann, 2008). They are a primary source of nutrition for other  
1082 amniotes. Functionally similar to vitellogenin, caseins have persisted in all mammalian milks  
1083 (Brawand et al., 2008). Active functioning of the yolk sac is restricted to the first trimester in  
1084 placental mammals, and it is postulated to provide nutrients to the embryo (Kuzima et al., 2023).  
1085 The detection of glycodelin in the yolk sac epithelium also supports this (Burton et al., 2002). In  
1086 the yolk-sac of bats, dogs, and non-human primates the mesoderm derived layer is absorptive  
1087 and may transfer substances from the exocoelomic cavity where the yolk sac is located (Enders  
1088 et al., 1976; Freyer & Renfree, 2009; King & Wilson, 1983; Lee et al., 1983).

1089 The morphology of the yolk-sac and process of vitellogenesis differs between birds and non-  
1090 avian reptiles. In birds, during the process of meroblastic cleavage, the zygote's cells divide  
1091 while the yolk component does not. The yolk forms a large, fluid, non-cellularized mass  
1092 surrounded by the extraembryonic yolk sac. The formation of the yolk-sac placenta in birds has

1093 the following pattern—first the bilaminar omphalopleure forms and then trilaminar  
1094 omphalopleure; blood vessels move into folds of the extraembryonic endoderm, becoming  
1095 stratified epithelium; the folds carrying the blood vessels reach the peripheral regions of the yolk  
1096 only and the center of the yolk mass remains uncellularized (Starck, 2021). Intensive  
1097 development of hemopoietic tissue surrounding the blood vessels during most of embryonic  
1098 development, thus far, appears to be unique to birds (Starck, 2021). Compared to non-avian  
1099 sauropsids, the unique pattern of yolk processing in birds facilitates faster embryonic  
1100 development (Blackburn, 2021).

1101 The yolk sac characteristic of non-avian reptilian eggs serves as a model for the transition  
1102 between the egg of anamniotes and amniotes (Blackburn, 2020). A series of recent papers,  
1103 covering species of snakes, lizards, crocodiles, and turtles, indicate that these taxa utilize similar  
1104 developmental pathways of yolk-sac formation and yolk processing that differs from birds  
1105 (Blackburn, 2020, 2021; Blackburn et al., 2019; Elinson et al., 2014; Elinson & Stewart 2014;  
1106 Stinnett et al., 2011). Across these taxa, a bilaminar/trilaminar omphalopleure overgrows the  
1107 yolk mass, and the yolk mass gets invaded by proliferating endodermal cells that phagocytose  
1108 the yolk material. These cells form clumps, progressively filling the yolk mass. Small blood  
1109 vessels derived from yolk sac vasculature invade the yolk sac cavity and the endodermal cells  
1110 arrange in monolayers around these vessels, forming “spaghetti bands” (Blackburn, 2021). The  
1111 yolk sac of *Pantherophis guttatus* is one suitable model for studying the transition of the yolk-  
1112 sac from anamniotes to amniotes (Elinson & Stewart, 2014; Elinson et al., 2014).

1113 A major difference between non-avian reptilian yolk-sac formation is the morphology and  
1114 extent of vascularization and cellularization in the yolk sac cavity (Starck, 2021). Birds have a  
1115 yolk-sac with absorptive endodermal lining that digests nutrients and send them into blood

1116 circulation (Starck, 2021) whereas snakes, lizards, turtles, and crocodylians have a yolk sac that  
1117 becomes invaded by endodermal cells that proliferate and phagocytose yolk material (Blackburn,  
1118 2021). In these taxa, yolk material becomes cellularized, digested, and transported by vitelline  
1119 vessels to the developing embryo (Blackburn, 2021). Factors involved with cellularization of the  
1120 yolk-sac are proposed to include cell cycle regulators and structural proteins (Elinson et al.,  
1121 2014). Generation of these cells are suspected to be reliant on processes of angiogenesis and are  
1122 likely transcriptionally active (Elinson et al., 2014). Few transcriptomic profiles of yolk-sac  
1123 placentas in reptiles have been documented to my knowledge (Griffith et al., 2016). Significant  
1124 overlaps in the yolk-sac transcriptomes of human, mice, and chicken—including apolipoproteins  
1125 and SLC transporters—however, suggest functional conservation (Cindrova-Davies et al., 2017).

1126 As discussed in a previous section, progesterone inhibits myometrial contractility, but it also  
1127 inhibits estrogen-induced hepatic vitellogenin synthesis (Custodia-Lora, Novillo, & Callard,  
1128 2004; Callard et al., 1992). Variable progesterone concentrations in circulation throughout  
1129 gestation in viviparous squamates may reflect a trade-off to allow estrogen expression to support  
1130 hepatic vitellogenin synthesis during embryonic development, thus supporting nutrient  
1131 provisioning during the lengthened embryonic retention. Although hepatic vitellogenesis usually  
1132 ceases during gestation, vitellogenin synthesis and mother-to-embryo transfer was detected in  
1133 one viviparous fish, *Xenotoca eiseni*, during gestation (Iida et al., 2019). Future research should  
1134 consider the timing of vitellogenin synthesis throughout the reproductive cycle in gestating and  
1135 non-gestating viviparous squamates to investigate this further.

1136

1137 (3) *Evolutionary history of placentrophy in mammals & squamates*

1138 Traditionally, it was thought that placentrophy evolved after viviparity in squamates  
1139 (Packard, Tracy, & Roth, 1977; Shine & Bull, 1979). Further research demonstrated that  
1140 placentrophy and viviparity evolved simultaneously (incipient matrotrophy) in mammals and  
1141 may have in squamates (Blackburn, 1985, 1992, 2005, 2006; Stewart & Eday, 2010). The  
1142 incipient matrotrophy model relies on evidence that 1) uterine provisioning of nutrients predates  
1143 the origin of viviparity (Blackburn 1985, 1992, 2006), 2) uterine and embryonic tissues have a  
1144 close anatomical and physiological association in viviparous taxa and 3) some degree of  
1145 placental transfer of organic or inorganic molecules occurs in viviparous taxa (Stewart & Eday,  
1146 2010). In squamates, the potential for both incipient matrotrophy and evolution of placentrophy  
1147 after viviparity is supported (Stewart & Eday, 2010). Facultative placental nutrient provisioning  
1148 and incipient matrotrophy may have driven the evolution of squamates with substantial  
1149 matrotrophic nutrient provisioning (Stewart, 2020; Swain & Jones, 2000).

1150 Placentation and implantation are not homologous in mammals compared to squamates  
1151 (Griffith, van Dyke & Thompson, 2013). Several placental specializations for gas and nutrient  
1152 exchange are unique to mammals including erosion of the uterine mucosa, extensively invasive  
1153 implantation, hemochorial contact, retention of a vascularized choriovitelline membrane, and  
1154 countercurrent patterns of blood flow (Blackburn, 2005). This enables extensive exchange of  
1155 nutrients in addition to water and gas. The vast majority of viviparous squamates have the most  
1156 superficial type of chorioallantoic placenta called epitheliochorial placenta (Blackburn, 1993).

1157 Nutrient provisioning through placentrophy is obligate for embryonic development in only  
1158 five lineages of squamates, all of which are scincid lizards (Blackburn, 2000; Flemming &  
1159 Blackburn, 2003; Ramírez-Pinilla et al., 2011; van Dyke et al., 2014). *Pseudemoia*  
1160 *pagenstecheri*, a lizard with a highly specialized placenta, out-performs lecithotrophic oviparous

1161 close relatives in the relative amount of nutrients it transfers to the embryo (Stewart et al., 2009).  
1162 *Pseudemoia entrecasteauxii* is a moderately matrotrophic viviparous skink, with roughly half of  
1163 embryonic nutrient uptake from the yolk and half through a specialized cyto-epitheliochorial  
1164 placenta (Adams et al., 2005; Speake et al., 2004; Stewart & Thompson, 1993, 2009).

1165 Specializations of the chorioallantoic placenta for nutrient provisioning in some squamates  
1166 include elaborate specializations for uterine secretion and absorption, including placentomes,  
1167 chorionic areolae, hypertrophied uterine mucosa, and chorionic epithelia modified for absorption  
1168 (Blackburn, 2005). In squamates, specializations for gas exchange across the chorioallantoic  
1169 placenta include decreased diffusion distance between maternal and fetal capillaries, uterine  
1170 vascularity, shell membrane deterioration, and modifications of both fetal and maternal blood  
1171 properties (Blackburn, 1998, 2005; Blackburn & Lorenz, 2003; Blackburn & Vitt, 2002).

1172 Mammalian placenta-specific genes have deep origins in vertebrates (Rawn & Cross, 2008).  
1173 Placentation to support viviparity likely employs genes that are ancestral to the chorioallantois.  
1174 However, one study that looked at placentation and gene expression across a small sample of  
1175 divergent amniotes found only one gene with a placentrophy-specific pattern of gene expression,  
1176 *DIO3* (Griffith, Brandley et al., 2017). In mammals, *DIO3* is an imprinted gene and  
1177 preferentially paternally expressed. The authors suggest that the gene may increase offspring  
1178 resource uptake during pregnancy in the horse and a viviparous lizard, *Pseudemoia*  
1179 *entrecasteauxii*, where it is recruited to the placenta (Griffith, Brandley et al., 2017).

1180

#### 1181 (4) Genes involved with embryonic water, gas, and nutrient transport

1182 Water transport in animals is regulated by a family of molecular water channels called  
1183 aquaporins (AQs or AQPs) (Borgnia et al., 1999). In humans, *AQP1*, *AQP3*, *AQP4*, *AQP8* and

1184 *AQP9* are found in the placenta but further research is needed to understand how these influence  
1185 water fluxes between maternal and fetal tissues (Damiano, 2011). Transcriptomic analysis on  
1186 uterine tissue of the gestating, viviparous skink, *Chalcides ocellatus*, reveal differential  
1187 expression of *AQP1*, *AQP3*, *AQP5*, *AQP6*, *AQP8*, *AQP9* and *AQP11* when compared to non-  
1188 gestating uteruses (Brandley et al., 2012). In birds, *AQP1* is expressed in the chorioallantoic  
1189 membrane, and it is suggested to influence angiogenesis throughout embryonic development  
1190 (Ribatti et al., 2002). In a viviparous lizard, *Pseudemoia entrecasteauxii*, *AQP8* and *AQP9* were  
1191 more highly expressed in the chorioallantoic placenta compared to the yolk-sac placenta (Griffith  
1192 et al., 2016). During gestation in both oviparous and viviparous populations of the reproductively  
1193 bimodal skink, *Saiphos equalis*, several genes involved with water homeostasis are upregulated  
1194 in the uterus including *AQP1*, *AQP3* and *AQP12B* (Foster et al., 2020). In uteruses of *Saiphos*  
1195 *equalis*, *AQP5* and *AQP8* are upregulated during oviparous late gestation compared to viviparous  
1196 late gestation. In sheep, *AQP3* is differentially expressed during gestation, where it serves a dual  
1197 role of water transport to the embryo and fetal urea export (Johnston et al., 2000). This is similar  
1198 to the function of *AQP9* in humans (Damiano, 2011). Immunocytochemistry reveals that *AQP1*  
1199 and *AQP3* are expressed in the uterus of the highly placentrophic South American scincid lizard,  
1200 *Mabuya sp.* (Wooding et al., 2010). In *Zootoca vivipara*, *AQP9* is upregulated at midgestation  
1201 (Recknagel et al., 2021a).

1202       Some molecules are implicated in the regulation of aquaporins including insulin (INS),  
1203 human chorionic gonadotropin (HcG), cyclic adenosine monophosphate (cAMP) and cystic  
1204 fibrosis transmembrane conductance regulator (CFTR) (Damiano, 2011). Genes predicted to be  
1205 involved with reproduction in *Anolis carolinensis* are enriched for the GO term for cAMP-  
1206 mediated signaling (Alföldi, Di Palma, et al., 2011). Further comparative research should be



1207 done to elucidate the functional differences of aquaporins in oviparous and viviparous amniotes  
1208 and how they relate to the differing conditions under which these embryos develop.

1209 Genes involved embryonic oxygen transport precede the origin of amniotes. Hemoproteins  
1210 arose in evolutionary history well before they were used for placental oxygen transfer (Hardison  
1211 1998). In mammals, adult (Alpha: HBA; Beta: HBB, HBD) and embryonic hemoglobins (Alpha:  
1212 HBZ, HBA; Beta: HBE, HBG, and HBH) are involved with oxygen transport (Carter, 2012).  
1213 Some of these are unique to eutherian mammals following a series of duplication events (Opazo  
1214 et al., 2008). However, fetal hemoglobins are found in turtles, lizards, and snakes (Pough, 1980).  
1215 HBA, HBB and HBM are all significantly downregulated in the uterine tissue of the viviparous  
1216 African Ocellated Skink, *Chalcides ocellatus*, during gestation compared to non-gestation  
1217 (Brandley et al., 2012). The oxygen demands of reptile embryos are relatively low until stage 30,  
1218 when most oviparous taxa oviposit (Shine & Thompson, 2006). In viviparous and oviparous  
1219 species with long egg retention, embryonic demand for maternal provision of oxygen and  
1220 removal of CO<sub>2</sub> increases at this stage.

1221 Improper water, gas and nutrient exchange can occur due to poor chorioallantoic blood flow  
1222 (Wootton et al., 1977). Thus, viviparous taxa require greater degrees of vascularization and  
1223 vasodilation to facilitate enhanced requirements for maternal resources compared to oviparous  
1224 taxa. Rather than increasing the size of the placenta, increasingly dense blood vessels can support  
1225 fetal growth without compromising space for embryonic growth as occurs in some pigs (Ford,  
1226 1997; Vonnahme et al., 2002). Embryonic vascularization and vasodilation are dependent on  
1227 signals from the endoderm (Jin et al., 2005; Vokes & Krieg, 2002; Wilt, 1965). In oviparous  
1228 individuals of *Saiphos equalis*, populations with extended egg retention, there is expansion of the  
1229 uterine vascular bed and thickening of the chorioallantoic tissue that supports increased

1230 embryonic growth in the later portion of oviparous gravidity (Parker et al., 2010). In the  
1231 viviparous scincid lizard, *Eulamprus quoyii*, angiogenesis, the formation of new blood vessels,  
1232 and expansion of the vessel-dense elliptical area of the uterus is associated with supporting  
1233 increased embryonic oxygen demand (Murphy et al., 2010).

1234       Several protein-coding genes are known to be involved with angiogenesis, vascularization,  
1235 and vasodilation in utero. One study that examined expression patterns across chickens  
1236 (oviparous), horses (viviparous), two viviparous squamates, and one oviparous squamate found  
1237 that no examined genes for angiogenesis showed a viviparity-specific expression pattern  
1238 (Griffith, Brandley et al., 2017). However, other than the chicken, the only oviparous taxa  
1239 included in this study was a reproductively bimodal skink, *Lerista bougainvillii* (Griffith,  
1240 Brandley et al., 2017). Alternatively, differential gene expression analyses on oviparous and  
1241 viviparous individuals of *Zootoca vivipara*, revealed pathways for angiogenesis enriched in  
1242 viviparous female reproductive tissues; and pathways for angiogenesis were enriched across  
1243 genes under divergent selection in oviparous and viviparous *Z. vivipara* individuals.

1244       In the uterine tissue of gestating viviparous skinks and rats, several genes for angiogenesis  
1245 are upregulated—*EPASI*, *HIF1A* and *VEGFA* (Brandley et al., 2012; Whittington et al., 2015,  
1246 2017). Other proteins involved in vascularization and vasodilation in utero include members of  
1247 the vascular endothelial growth factor (*VEGF*) gene family, VEGF receptors (*VEGFRs*),  
1248 placental growth factor (*PGF*) and nitric oxide synthase (*NOS*) (Blomberg et al., 2010; Chen,  
1249 Wang et al., 2015; Gilbert, 2010; Reynolds et al., 2006; Risau, 1997; Torry et al., 2003;  
1250 Vonnahme et al., 2001). In *Saiphos equalis*, different homologs of *NOS* experience different  
1251 patterns of gene expression across the oviparous and viviparous stages of gestation/gravidity  
1252 (Foster et al., 2020). One homolog of *NOS* is upregulated during oviparous late gestation, and

1253 another is upregulated during viviparous late gestation (Foster et al., 2020). Several genes  
1254 involved with angiogenesis and vascular morphogenesis are downregulated in the pre-  
1255 implantation uterus of a marsupial, the Fat Tailed Dunnart, *Sminthopsis crassicaudata*—  
1256 *ADGRA2, ADGRB2, ANGPTL1, EPHB4, ISM1, PDZRN3, RHOJ, TNMD,* and *VEGFD*  
1257 (Whittington et al., 2018).

1258 In humans, immune factors are also responsible for increasing embryonic blood supply.  
1259 Embryonic non-classical MHC class I molecule, HLA-G, and uterine natural killer (uNK) cells  
1260 support increased embryonic blood supply (Moffett & Loke, 2006; Rajagopalan et al., 2006). A  
1261 similar pattern of utilizing immune properties to support embryonic blood supply has not been  
1262 yet identified in squamates.

1263 Lipids are a main energy source for embryos. Lipoprotein lipase (LPL) is an important  
1264 enzyme in lipid transport. LPL is significantly expressed on the syncytiotrophoblasts, specialized  
1265 placental cells, of humans (Lindegaard et al., 2005) and the endometrium of cows (Forde et al.,  
1266 2011), and pigs (Ramsay et al., 1991), where it plays a role in lipid mobilization. A viviparous  
1267 lizard, *Pseudemoia entrecasteauxii*, increases capacity for lipid transport toward the end of  
1268 pregnancy (Griffith, van Dyke & Thompson, 2013). The uterine tissue of the yolk-sac placenta in  
1269 this species had significantly higher expression of LPL than the uterine tissues of the  
1270 chorioallantoic placenta (Griffith, van Dyke & Thompson, 2013), leading the authors to suggest  
1271 that the yolk-sac placenta is the major site of lipid transport. LPL expression was not detected  
1272 during pregnancy in the viviparous skink, *Chalcides ocellatus* (Blackburn, 1992; Brandley et al.,  
1273 2012). Instead, lipid transport may be facilitated by fatty acid binding proteins in this species  
1274 (Chmurzyńska, 2006; Brandley et al., 2012). These are also active on mammalian placenta  
1275 (Haggarty, 2002).

1276 Apolipoproteins are also suitable candidates for transport of fatty acids, cholesterol, and  
1277 phospholipids. Five of these (*APOA1*, *APOA2*, *APOA4*, *APOE*, and *APOM*) and *APOA1BP* are  
1278 significantly upregulated in the pregnant uterus of the viviparous skink, *Chalcides ocellatus*  
1279 (Brandley et al., 2012). *APOA1BP* is also upregulated in the uterus of the chorioallantoic  
1280 placenta and yolk-sac placenta compared to non-gestational uterine tissues in *Pseudemoia*  
1281 *entrecaeauxii* (Griffith et al., 2016). Additionally, upregulation of 136 genes that encode solute  
1282 carrier proteins (SLCs) in the pregnant uterus of *Chalcides ocellatus* are associated with  
1283 transport of inorganic ions, metals, glucose, amino acids, peptides, fatty acids, and carboxylic  
1284 acids (Brandley et al., 2012).

1285 Supply of amino acids is required for embryonic development. SLCs have important  
1286 transport functions, including the transport of amino acids, and thus they are considered to be  
1287 important for gestation (Foster et al., 2022). However, a recent study found no overlap in the  
1288 amino acid transporting SLCs upregulated in placentas of viviparous placentrophic vertebrates  
1289 studied, which included eight representatives from Mammalia, Reptilia, and Chondrichthyes  
1290 (Foster et al., 2022). However, *SLC38A3* was upregulated in all viviparous species except *Rattus*  
1291 *norvegicus* (Foster et al., 2022).

1292 Cathepsins and phospholipases are important for uterine secretions for embryonic  
1293 development in horses, pigs, sheep, and cattle (Bazer, 1975; Satterfield et al., 2007; Song et al.,  
1294 2010). Cathepsins are present in yolk sacs of humans and mice. They function to degrade  
1295 proteins to free amino acids (Cindrova-Davies et al., 2017). Two genes for cathepsin L (*CTSL1*  
1296 and *CTSL2*) are upregulated in the uterus during gestation in *Chalcides ocellatus* (Brandley et al.,  
1297 2012). *CTSL* is also upregulated in the uterus during the pre-implantation phase in the Fat-Tailed  
1298 Dunnart, *Sminthopsis crassicaudata* (Whittington et al., 2018), and in the uterus of the

1299 chorioallantoic placenta and uterus of the yolk sac placenta during gestation in *Pseudemoia*  
1300 *entrecasteauxii* (Griffith et al., 2016).

1301 In viviparous individuals of the reproductively bimodal lizard, *Saiphos equalis*, many genes  
1302 for cellular adhesion are upregulated during late gestation (Foster et al., 2020). The authors  
1303 postulated that this helps facilitate maternal-fetal signaling and paracellular transport (Foster et  
1304 al., 2020). Gao et al. (2019) identified a set of genes in *Phrynocephalus vlangalii* that were  
1305 differentially expressed in the uterus during the stage of placentation and these enriched GO  
1306 terms functionally related to the process of placentation. This included an estrogen receptor  
1307 (*ESRI*) and two growth factor receptors (*GHR* and *IGFIR*) (Gao et al., 2019).

1308 Finally, the proteomes of the ovary and placenta from obligately placentrophic *Mabuya*  
1309 lizards can further serve as a useful resource for examining nutrient provisioning in squamates  
1310 (Hernández-Díaz et al., 2017). In the placenta they found protein expression involved with  
1311 nutrient metabolism, transport, protein synthesis, and embryonic development (Hernández-Díaz  
1312 et al., 2017).

1313

#### 1314 (5) Uterine glands: adenogenesis, placenta development and histotrophy

1315 In addition to their role in eggshell deposition in oviparous taxa, uterine glands also secrete  
1316 growth factors and cytokines that support placental development in mammals. In humans, these  
1317 include transforming growth factor- $\beta$  (TGF- $\beta$ ), epidermal growth factor (EGF), vascular  
1318 endothelial growth factor (VECG), and leukemia inhibitory factor (LIF) (Hempstock et al.,  
1319 2004). In eutherians, TGF- $\beta$  supports placental development by regulating proliferation and  
1320 invasion rates of placental cells lines (Caniggia et al., 2000; Hempstock et al., 2004; Lafontaine  
1321 et al., 2011).

1322 Histotrophy (also called histiotrophy) occurs when nutrients are secreted into the uterine  
1323 lumen from vesicles of the columnar epithelial cells of the uterus and taken up by the embryo.  
1324 Histotrophic nutrient provisioning is documented across amniotes including marsupials  
1325 (Whittington et al., 2018), several ungulate taxa (Bazer et al., 2011; Han et al., 2016; Gao et al.,  
1326 2009), humans (Burton et al., 2002), and appear to occur in some viviparous squamates (van  
1327 Dyke et al., 2014). In humans, histotrophic nutrient provisioning occurs during the first trimester.  
1328 The intervillous space is filled with fluid containing uterine gland secretions that get  
1329 phagocytosed by the syncytiotrophoblasts and are the initial nutrient source for the fetus (Burton  
1330 et al., 2002). Two of these glycoproteins are epithelial mucin (*MUC1*) and glycodefin A (*GdA*)  
1331 (Burton et al., 2002). Interestingly, the *MUC15* gene is upregulated during gravidity/gestation in  
1332 the uterus of oviparous and viviparous *Saiphos equalis* individuals (Foster et al., 2020). This also  
1333 occurs in the chorioallantoic placenta of *Pseudemoia entrecasteauxii* during gestation (Griffith et  
1334 al., 2016). Several mucins are expressed in the uterus in non-gravid and gravid samples from  
1335 oviparous individuals of *Lerista bougainvillii* and *Lampropholis guichenoti* (Griffith et al.,  
1336 2016).

1337 A survey of viviparous squamates with modest to extensive placentrophy revealed  
1338 prevalence of histotrophic nutrient provisioning rather than hemotrophy, transfer of nutrients  
1339 between maternal and fetal blood streams (Blackburn 2015). Embryos of *Chalcides chalcides*  
1340 have extensive placentrophy that supports substantial maternal nutrient provisioning and  
1341 histotrophy (Blackburn, 2015a). Histotrophy may lessen parent-offspring conflict and give the  
1342 mother the control over nutrient provisioning compared to hemotrophy (Blackburn, 2015b).

1343 *Chalcides ocellatus* has less extensive placentrophy than *C. chalcides* but the gestating uterus  
1344 still illustrates expression of many genes associated with organic and inorganic nutrient transport

1345 (Blackburn, 2015a). Multiple *TGF- $\beta$*  genes are differentially expressed in the uterus during  
1346 gestation in *C. ocellatus*, however most these are downregulated compared to non-gestational  
1347 uterine tissue (Murphy et al., 2012). The influence of *TGF- $\beta$*  on placental development and  
1348 nutrient provisioning in *Chalcides spp.* remains to be explored to my knowledge. A TGF- $\beta$   
1349 receptor (*TGFBRI*) was associated with placental development in *Phrynocephalus vlangalii*  
1350 (Gao et al., 2019).

1351 Essential to histotrophy is adenogenesis, the generation of endometrial glands. Adenogenesis  
1352 allows for the secretion of histotrophs. The period of early development during which  
1353 adenogenesis occurs is highly variable among vertebrates but it is required for embryonic  
1354 survival (Gray et al., 2001, 2002; Spencer & Bazer, 2004). Some genes involved with  
1355 adenogenesis in sheep are insulin-like growth factor 1 (*IGF-1*), *IGF-2*, *PAX2*, *LHX1* (also known  
1356 as *LIM1*) and *EMX2*, genes in the abdominal-B HOXA cluster, members of both *Wnt* and  
1357 Hedgehog (*Hh*) gene families (Fazleabas et al., 2004), prolactin (*PRL*), fibroblast growth factor 7  
1358 (*FGF7*), *FGF10*, *FGFR2IIIb*, hepatocyte growth factor (*HGF*), a receptor tyrosine kinase (*c-*  
1359 *Met*), and cadherins (Fazleabas, 2007).

1360 In the gestating uterus of *Chalcides ocellatus*, insulin-like growth factor-binding protein 5  
1361 (*IGFBP5*) is one of the most significantly downregulated genes compared to non-gestational  
1362 uterine tissue (Brandley et al., 2012). *IGFBP5* is evolutionarily conserved and multifunctional,  
1363 with an important role in regulating IGF signaling, including that of *IGF-1* and *IGF-2* (Duan &  
1364 Allard, 2020). Other than adenogenesis in sheep, IGFs serve an important role in the growth of  
1365 fetal and maternal tissues in mammals (Gibson et al., 2001; Kampmann et al., 2019).

1366 Genes involved with histotrophic secretion in the marsupial *Sminthopsis crassicaudata*  
1367 include *AP4SI*, *HYOU1*, and *SRPRA* (Whittington et al., 2018). Nutrient transporters

1368 significantly upregulated at this time are *APOL6* (cholesterol transport (Baardman et al., 2013)),  
1369 *PLA2G10* (hydrolysis of fatty acids during pregnancy (Miele et al., 1987)) and a wealth of SLCs  
1370 (solute carrier proteins for transport of sugar, ions, anions, glucose, fatty acids, calcium and zinc  
1371 (Whittington et al., 2018)). Subsequent research has identified downregulated of *HYOUI* at early  
1372 and mid-gestation; and downregulation of *SRPRA* at mid-gestation in viviparous *Zootoca*  
1373 *vivipara* compared to oviparous (Recknagel et al., 2021a). In a reproductively bimodal skink,  
1374 *Saiphos equalis*, *PLA2G10* is upregulated during viviparous late gestation compared to oviparous  
1375 late gestation (Foster et al., 2020). Upregulation of SLCs also occurs in the viviparous skink  
1376 *Chalcides ocellatus* (Brandley et al., 2012; Van Dyke et al., 2014) and in the uterus during  
1377 pregnancy in the grey short-tailed opossum, *Monodelphis domestica* (Hansen, Schilkey & Miller,  
1378 2016).

1379 Uterine glands are also important for secretions of eggshell precursors. I speculate that genes  
1380 involved with adenogenesis of uterine glands may be similarly used to support histotrophic  
1381 nutrient provisioning during transitions to viviparity, but further research is necessary.

1382 Specialized uterine areolar glands are found in some *Mabuya* lizards, a genus with oviparous  
1383 species and viviparous species that utilize placentrophy and histotrophy (Corso et al., 1988,  
1384 2000; Jerez & Ramírez-Pinilla, 2001; Ramírez-Pinilla, 2006; Vieira et al., 2007; Visser, 1975).

1385 Transcriptomic research focused on histotrophic nutrient provisioning, placental development,  
1386 and secretions of eggshell precursors in oviparous and viviparous *Mabuya spp.* would  
1387 complement literature on the genus.

1388

1389 (6) *Discussion & future directions—embryonic nutrients, gas, and water supply*



1390 Many genes for placental functions in mammals have deep origins in vertebrates (Rawn &  
1391 Cross, 2008). In pairwise comparisons of different viviparous amniotes, there is overlap in  
1392 hormones and proteins (SLC superfamily, insulin-like growth factors, aquaporins and solute  
1393 carrier proteins, etc.) involved in uterine remodeling, placentation, and placental transport. While  
1394 shared genes are recruited to the uterus across viviparous amniotes (Recknagel et al 2021a), there  
1395 are no shared genes recruited to the placenta across viviparous reptiles, mammals, and sharks  
1396 (Foster et al., 2022). Evolutionarily, this suggests higher conservation of the regulatory networks  
1397 associated with uterine responses to viviparity than placental responses to viviparity. The  
1398 relationship of these findings to embryonic nutrient provisioning and the evolution of the  
1399 amniotic egg requires further investigation. Supplementary Table 2 illustrates how genes  
1400 mentioned in text for water, gas, and nutrient transport are expressed in reproductive tissues of  
1401 squamates during gestation and gravidity.

1402 If specific genes or physiological processes impact more than one of the Main Five  
1403 categories, it could have a disproportionate influence on transitions. Such an overlap has already  
1404 been identified in *Zootoca vivipara*, where 11 genes are associated with both eggshell traits and  
1405 gestation length (Recknagel et al., 2021a). The solute carrier (*SLC*) gene superfamily is involved  
1406 with both nutrient transport (Brandley et al., 2012; Whittington et al., 2018) and eggshell  
1407 deposition (Yang et al., 2020). Adenogenesis is essential for histotrophic nutrient provisioning  
1408 and secretion of eggshell precursors. Additionally, progesterone production influences both  
1409 uterine quiescence, which is an important state to maintain in lengthened embryonic retention,  
1410 and it also inhibits hepatic vitellogenesis, an important process for lecithotrophic nutrient  
1411 provisioning. Thus, examining the role of *SLC* gene superfamily members, processes of

1412 adenogenesis, and progesterone production during embryonic development in oviparous and  
1413 viviparous squamate may reveal how interconnectivity of the Main Five are.

1414

## 1415 **V. Embryonic Calcium Provisioning**

1416

1417 The embryonic growth stage requires the greatest demand of calcium (Ecay et al., 2017;  
1418 Packard & Packard, 1984; Stewart & Ecay, 2010). To support this, peak uterine concentrations  
1419 of calcium are highest during either eggshell deposition or during the embryonic growth stage, in  
1420 oviparous and viviparous taxa, respectively (Linville et al., 2010; Stewart et al., 2009).  
1421 Regardless of parity mode, embryonic metabolism drives calcium uptake (Packard & Packard,  
1422 1984). The calcium source(s) utilized have clade-specific implications on the genomic and/or  
1423 physiological changes required to transition between parity modes.

1424

### 1425 *(1) Phylogenetic context of embryonic calcium sources*

1426 Calcium can be acquired by the embryo in three forms: calcium carbonate in the eggshell,  
1427 calcium bound to proteins and lipids in the yolk, and/or free ionic calcium from maternal  
1428 delivery through the placenta (Stewart & Ecay, 2010). These correspond with five calcium  
1429 mobilization patterns: 1) Birds, turtles and crocodiles predominately depend on the eggshell; 2)  
1430 Most squamates, regardless of parity mode, predominately depend on the yolk; 3) Some  
1431 squamate species are reliant on both the eggshell and yolk; 4) Some viviparous squamate species  
1432 are reliant on both the yolk and placenta; and 5) therian mammals and rare viviparous squamates  
1433 predominately depend on the placenta (Blackburn, 2015a; Hoenderop, Nilius, & Bindels, 2005;  
1434 Jenkins & Simkiss, 1968; Kovacs, 2015; Packard, 1994; Packard & Seymour, 1997; Stewart et

1435 al., 2009, 2009; Stewart & Ecy, 2010; Thompson, Stewart et al., 1999; Thompson, Stewart, &  
1436 Speake, 2000; Ramírez-Pinilla, 2006).

1437 From an evolutionary perspective, squamate eggs might serve as the best models of the  
1438 ancestral amniote egg. Unlike birds, oviparous squamates generally rely on yolk calcium rather  
1439 than eggshell calcium. The yolk sac of non-avian reptiles is a good model for the transition  
1440 between the egg of anamniotes and amniotes (Blackburn, 2020). Taken together and given that  
1441 hard calcified eggshells of Archelosaurs are likely derived (as discussed in section III.3)—  
1442 squamate eggs may have the closest resemblance to the ancestral amniote egg. Interestingly, to  
1443 my knowledge, oviparous squamates do not sequester calcium from the eggshell into the yolk  
1444 during incubation (Packard, 1994).

1445

1446 *(2) Hypotheses on calcium mobilization and the evolution of parity modes*

1447 It was hypothesized that predominant reliance on eggshell calcium should constrain lineages  
1448 to oviparity because the evolution of viviparity would result in a lost calcium source (hereafter  
1449 eggshell calcium constraint hypothesis) (Stewart & Ecy, 2010; Packard et al., 1977; Packard &  
1450 Packard, 1984). This hypothesis suggested that viviparity should only evolve in lineages  
1451 predominately reliant on yolk calcium (Packard et al., 1977; Packard & Packard, 1984).

1452 Fittingly, birds, turtles and crocodilians generally rely on eggshell calcium, and they are  
1453 constrained to oviparity (Anderson et al., 1987). The eggshell calcium constraint hypothesis  
1454 holds true for most viviparous squamates that rely heavily on yolk calcium (Stewart & Castillo,  
1455 1984; Stewart & Ecy, 2010; van Dyke et al., 2014).

1456 Subsequent research revealed that viviparity is not constrained by a prerequisite reliance on  
1457 yolk calcium. Oviparous scincid skinks studied thus far are intermediately reliant on eggshell and

1458 yolk calcium (Linville et al., 2010; Shadrix et al., 1994; Stewart et al., 2009; Stewart &  
1459 Thompson, 1993; Thompson et al., 2001). Calcium placentrophy contributes substantially to  
1460 embryonic development in several viviparous squamates including *Pseudemoia entrecasteauxii*,  
1461 *Eulamprus quoyi*, *Zootoca vivipara*, *Saiphos equalis*, and a species of *Mabuya* lizard (Ecay et al.,  
1462 2017; Linville et al., 2010; Ramírez-Pinilla, 2006; Ramírez-Pinilla et al., 2011; Stewart &  
1463 Thompson, 1993). These taxa, with the exception of *Zootoca vivipara*, are in the family  
1464 Scincidae (Burbrink et al., 2020), which is also the family with the most independent origins of  
1465 viviparity in squamates (Blackburn, 1982, 1999; Pyron & Burbrink, 2014).

1466 To understand the breadth of physiological conditions from which oviparity and viviparity  
1467 evolve in squamates, future research should examine calcium transport in other lineages. Studies  
1468 focused on snakes would be particularly informative given the sparse literature on them.

1469 *Helicops angulatus*, a reproductively bimodal water snake from South America, is an ideal  
1470 model for this (Braz et al., 2016). Thus far, many oviparous snakes are known to be  
1471 intermediately reliant on yolk and eggshell calcium. This has not precluded viviparity from  
1472 evolving in these lineages.

1473 The presence of embryos during extended embryonic retention may trigger positive feedback  
1474 stimuli for continued uterine calcium secretions which may support placental calcium transport,  
1475 and thus incipient calcium matrotrophy (Stewart & Ecay, 2010). This is postulated to resemble  
1476 the hormonal and mechanical stress mechanisms implicated in avian eggshell formation and  
1477 uterine calcium secretions (Bar, 2009a; Stewart & Ecay, 2010). The influx of calcium late in  
1478 viviparous gestation may be triggered in part by embryonic growth that over distends the uterus.  
1479 This is seen in studies on myometrial stretch in mammals when uterine overdistention triggers  
1480 spikes in calcium (Kao & McCullough, 1975; and see e.g. Wray et al., 2015).

1481       Dramatic changes to activity in chorioallantois should not be required during parity mode  
1482 transitions because these homologous tissues (Metcalf & Stock, 1993) transport calcium  
1483 regardless of parity mode (Ecay, Stewart & Blackburn, 2004; Tuan & Scott, 1977; Tuan &  
1484 Knowles, 1984; Tuan et al., 1978, 1986). Specialized placental structures in some viviparous  
1485 squamates enhance calcium provisioning but specialization is not required for placental calcium  
1486 transport (Stewart et al., 2009; Stewart & Ecay, 2010; Thompson et al., 2000). Loss of  
1487 chorioallantoic calcium transporting capacity would be disadvantageous to either parity mode.  
1488 Growing research reveals that, like mammals, placentrophy and viviparity can evolve  
1489 concurrently in squamates (Blackburn, 2015a; Ecay et al., 2017; Stewart & Ecay, 2010).

1490       Placing these previously proposed models in a phylogenetic context, the calcium transport  
1491 method of oviparous ancestors likely has an influence on the method of calcium transport used  
1492 for viviparous taxa—matrotrophic calcium provisioning, lecithotrophic calcium provisioning, or  
1493 a combination of the two. Consistent with the basal cap hypothesis—when viviparity arises from  
1494 oviparous ancestors with embryos that depended predominately on eggshell calcium, this should  
1495 favor a transition to viviparity via incipient calcium matrotrophy because the chorioallantois  
1496 already plays the major role in transporting calcium from the eggshell to the embryo. Since the  
1497 reproductive mode and calcium provisioning of oviparous ancestors are essentially unknown,  
1498 researchers can use the closest oviparous relatives as proxies. Similarly, viviparous taxa that are  
1499 in close phylogenetic proximity to oviparous taxa that depend on lecithotrophic calcium  
1500 provisioning should remain reliant on yolk calcium. Together, these guidelines provide a  
1501 framework from which researchers can form hypotheses about the calcium provisioning method  
1502 of a viviparous lineage if the calcium provisioning method of oviparous close relatives are  
1503 known, or vice versa. Measurements of the proportional contribution of different calcium sources

1504 during development has only been done in select taxa (e.g. Packard, 1994; Stewart, 2013;  
1505 Stewart & Ecy, 2010; Stewart, Ecy & Blackburn 2004). Once validated, the framework (i.e.,  
1506 the calcium provisioning method of close relatives) can help increase the speed at which science  
1507 measures and infers the evolutionary history of calcium provisioning across amniotes and  
1508 squamates. Collection of this data across the squamate phylogeny may enable assignment of  
1509 these hypotheses to specific clades.

1510 Embryonic calcium source could have implications on the physiological changes required to  
1511 transition between parity modes. Reliance on yolk calcium should render, essentially, no  
1512 mechanistic changes for calcium transport. On the other hand, incipient calcium matrotrophy  
1513 requires regulatory changes in the uterus, like timing of calcium secretions (Griffith et al., 2015).  
1514 However, regardless of parity mode 1) the uterus secretes calcium, 2) the chorioallantois  
1515 transports calcium and 3) embryonic metabolism drives uptake of calcium. Assuming maternal  
1516 tissue remains responsive to embryonic metabolism, the joint evolution of matrotrophic calcium  
1517 provisioning with viviparity may require little to no physiological adjustments.

1518 The diversity of embryonic calcium provisioning patterns in viviparous squamates may not  
1519 be fully explained by the eggshell calcium constraint hypothesis (Packard et al., 1977; Packard &  
1520 Packard, 1984) or incipient calcium matrotrophy (Stewart & Ecy, 2010). Both hypotheses  
1521 implicitly assume that viviparity equates to a lost eggshell. In one viviparous squamate, *Haldea*  
1522 *striatula*, and in viviparous populations of two reproductively bimodal lizards, *Zootoca vivipara*  
1523 and *Saiphos equalis*, the calcified eggshell is considered as a component of the placenta (Stewart,  
1524 2013). Some other viviparous squamates have transient calcified patches on their embryonic  
1525 membranes (Blackburn, 1998; Heulin, 1990, 2005; Qualls, 1996) suggesting that uterine calcium  
1526 secreting capabilities in early gestation may be retained in some viviparous lineages. In the case

1527 of reversals, it remains unknown how the uterus shifts back to early calcium secretions after  
1528 ovulation (Blackburn, 2015b; Griffith et al., 2015).

1529

### 1530 (3) *Embryonic calcium provisioning mechanisms*

1531 In vertebrates, specialized tissues that recover environmental calcium and transport it into  
1532 blood circulation maintain conserved mechanisms for intracellular calcium transport (Bronner  
1533 2003; Hoenderop et al., 2005). These include the uterus, chorioallantoic tissues, and yolk  
1534 splanchnopleure (Bronner, 2003; Hoenderop et al., 2005; Stewart, 2013). Therefore, uterine and  
1535 embryonic tissues may be pre-adapted for maternal and embryonic calcium provisioning.

1536 In birds, a sub-compartment of the mammillary layer of the eggshell is the calcium reserve  
1537 body (Chien et al., 2009), which contains microcrystals of calcite that get dissolved and  
1538 transported as calcium to the embryo (Chien et al., 2009). Calcium is eroded from the eggshell  
1539 by acid released from villus cavity cells (VCCs) in chorioallantoic membrane (Anderson, Gay,  
1540 and Schraer, 1981; Narbaitz et al., 1981; Packard & Lohmiller, 2002; Simkiss, 1980). This  
1541 increases the carbonic anhydrase activity of the cells enabling calcium to be released into the  
1542 cavity between the eggshell and the chorionic epithelium, where it is taken up by capillary  
1543 covering cells (CCCs) in chorioallantoic membrane (Coleman & Terepka, 1972). In some  
1544 species this erosion leads to a gradual weakening of the eggshell that facilitates hatching (Chien,  
1545 Hincke & McKee, 2008). In chickens, transcalcin, a calcium binding protein, is credited for the  
1546 calcium transporting capacity of the chorioallantoic membrane (Tuan & Knowles, 1984; Tuan &  
1547 Ono, 1986; Tuan & Scott, 1977; Tuan et al., 1978, 1986). The presence of VCCs and CCCs in  
1548 the chorioallantois of viviparous squamates would indicate a known route through which calcium  
1549 can be absorbed.

1550 Transcellular calcium transport has been modeled as a three-step process involving proteins  
1551 calbindin-D9K, calbindin-D28K, and the highly calcium-specific ion channels of the transient  
1552 receptor potential vanilloid gene family (*TRPV5* and *TRPV6*) (Stewart & Ecaj, 2010). Across  
1553 vertebrates, this machinery is shared in epithelial tissues with significant roles in calcium  
1554 transport (Hoenderop et al., 2005). Estrogen and vitamin D3 have regulatory roles in this  
1555 process.

1556 Calbindin-D9K, calbindin-D28K, *TRPV5*, and *TRPV6* is involved with calcium exchange in  
1557 multiple organs of birds, squamates, and mammals. Broadly, activity of calbindin-D9K and/or  
1558 calbindin-D28K is associated with patterns of calcium absorption in the mammalian kidney and  
1559 uterus (Bindels, 1993; Luu et al., 2004), murine uterus and placenta (Lafond & Simoneau, 2006;  
1560 Koo et al., 2012), and chicken duodenum and uterus (Bar, 2009b; Yang et al., 2013). In humans,  
1561 calbindin-D9K and calbindin-D28K are critical to the active transport of Ca<sup>2+</sup> across placental  
1562 cells (Faulk & McIntyre, 1983; Belkacemi, Simoneau & Lafond, 2002; Belkacemi et al., 2004).  
1563 A study on rats suggests that calbindin-D9K increases by over 100-fold in the last 7 days of  
1564 gestation (Glazier et al., 1992), when the embryo gains the majority of calcium. *TRPV6* is  
1565 involved with maternal-fetal calcium transport in mice (Suzuki et al., 2008). Increased *TRPV6*  
1566 and calbindin-D28K expression occurs during eggshell formation in chickens (Yang et al.,  
1567 2013). Given the involvement of these genes in both eggshell deposition and embryonic calcium  
1568 transport, squamates may have exploited this pathway to support transitions. Expression of these  
1569 genes during gestation or gravidity in squamates has been detected (e.g. calbindin-d9K in  
1570 *Saiphos equalis*, and calbindin-d28k in *Zootoca vivipara*) (Foster et al., 2020; Recknagel et al.,  
1571 2021a), and is expanded upon in the following paragraphs.



1572 In several highly matrotrophic lizards, embryonic uptake of calcium is associated with  
1573 placental expression of calbindin-D28K (Stewart et al., 2009; Stinnett et al., 2011, 2012). In both  
1574 oviparous and viviparous embryos of *Zootoca vivipara*, sharp increase in calcium uptake in late  
1575 development coincides with increased calbindin-D28K and PMCA by the chorioallantois  
1576 (Stewart et al., 2009, 2011). In oviparous corn snakes, *Pantherophis guttatus*, expression of  
1577 calbindin-D28K in the yolk-sac and chorioallantoic membrane coincides with growth of these  
1578 tissues and calcium transport activity (Ecay et al., 2004). The chorioallantois of other lizards and  
1579 snakes transport calcium to the embryo and express calbindin-D28K and PMCA (Blackburn,  
1580 2004; Ecay et al., 2004; Stewart et al., 2010; Stinnett et al., 2012).

1581 Viviparous embryos of *Zootoca vivipara*, a reproductively bimodal lizard, incubated *ex utero*  
1582 respond to availability of calcium by increasing expression of calbindin-D28K (Ecay et al.,  
1583 2017). In this species, embryonic recognition of environmental calcium stimulates a transcellular  
1584 calcium transporting mechanism and may also alter chorioallantoic membrane paracellular  
1585 permeability to calcium (Ecay et al., 2017). The authors proposed that there is a calcium sensing  
1586 receptor (CaSR) on chorionic epithelial cells to support this in both oviparous and viviparous  
1587 *Zootoca vivipara* embryos (Ecay et al., 2017), similar to the CaSRs expressed by vertebrate cells  
1588 involved in calcium homeostasis (Brennan et al., 2013).

1589 As mentioned earlier, PMCA activity is associated with eggshell deposition in birds and  
1590 oviparous squamates (Bar, Rosenberg, & Hurwitz, 1984; Hincke et al., 2012; Wasserman et al.,  
1591 1991). PMCA is also crucial for calcium transport in late embryonic development in rats (Glazier  
1592 et al., 1992). In viviparous scincid lizards, *Niveoscincus metallicus*, *N. ocellatus*, and  
1593 *Pseudemoia spenceri*, PMCA was expressed in uterine glandular and surface epithelia during  
1594 pregnancy but only *P. spenceri* expressed it throughout gestation (Herbert et al., 2006). When

1595 PMCA was not detected by immunoblotting in the yolk splanchnopleure of *Haldea striatula*, a  
1596 viviparous snake that relies predominately on yolk calcium (Stewart, 1989; Fregoso, Stewart, &  
1597 Ecay, 2010), NCXs were proposed as an alternative transporter of calcium (Fregoso et al., 2012).  
1598 NCXs are important for placental calcium transport in humans (Belkacemi et al., 2005).

1599        Calcitropic hormones, those involved with calcium transport, and phosphotropic hormones,  
1600 those involved with phosphorous transport, operate via an interconnected pathway (Andrukhova  
1601 et al., 2016; Biber, Hernando & Forster, 2013; Blaine, Chonchol & Levi, 2015; Erben &  
1602 Andrukhova, 2015). Phospho- and calcitropic hormones are important regulators of fetal serum  
1603 mineral concentrations (Kovacs, 2015). Evidence from viviparous amniotes suggests that these  
1604 are suitable candidates for embryonic calcium provisioning. In mice, genes encoding parathyroid  
1605 hormone (*PTH*) and *PTH*-related peptide (*PTHrP*) are important regulators of placental calcium  
1606 transport (Kovacs et al., 1996; Simmonds et al., 2010). A non-exhaustive list of additional  
1607 candidates for embryonic calcium provisioning include fibroblast growth factor 23 (Bar, 2009a;  
1608 Erben & Andrukhova, 2015; Stewart & Ecay, 2010), the annexin gene family (Matschke et al.,  
1609 2006), carbonic anhydrase (Narbaitz et al., 1981; Tuan & Knowles, 1984), and calcium binding  
1610 proteins (CaBPs) can be found in the referenced literature.

1611

1612        (4) *Discussion & future directions—calcium provisioning and parity mode evolution*

1613        Phylogenetic frameworks enable researchers to make broader testable hypotheses about the  
1614 evolutionary history of calcium provisioning in specific clades. Such a framework is proposed in  
1615 section V.2 to infer ancestral parity modes in the context of calcium provisioning in amniotes.  
1616 Implications gleaned from taxon-specific studies can be explored in distantly related analogous  
1617 groups.

1618 Genes involved with calcium transport in uterine and embryonic tissues have been described  
1619 across mammals, birds, and reptiles. Like other amniotes, activity of calbindin-D28K and PMCA  
1620 supports embryonic calcium provisioning across diverse oviparous and viviparous squamates.  
1621 Their involvement with both eggshell deposition and embryonic calcium provisioning makes  
1622 these particularly interesting candidates for parity mode evolution. The regulatory influence of  
1623 other molecules in calcium transport, like *PTH*, *PTHrP* and NCXs has not been evaluated  
1624 thoroughly in squamates. Additional reviews on mechanisms of embryonic calcium provisioning  
1625 in squamates can be found in the literature (Stewart, 2013; Stewart & Eday, 2010).

1626 Additionally, I add a speculation. Perhaps lineages with incipient calcium matrotrophy more  
1627 feasibly reverse to oviparity because of the continued role of the uterus in calcium provisioning.  
1628 However, this hypothesis only holds up if maternal provisioning of calcium is not synonymous  
1629 with maternal provisioning of all nutrients.

1630

## 1631 **VI. Maternal-Fetal Immune Dynamics**

1632

1633 Medawar (1953) pointed out the paradigm between the peripheral body's normal attack  
1634 response to allografts (foreign tissue) and uterine tolerance to embryos (Medawar, 1953). This  
1635 was inspired by earlier work by Ray Owen (Owen, 1945). Stricter regulation of the maternal and  
1636 fetal immune systems is expected for viviparous reproduction because of contact between uterine  
1637 and embryonic tissues. Oviparity may pose less of an immunological challenge. Medawar  
1638 suggested barriers, inertness and/or immunosuppression enable pregnancy. This formed the  
1639 foundation of decades of medical research on immune dynamics between maternal, embryonic,  
1640 and paternal immune factors in utero.

1641 In recent years, there was a call for a reappraisal of Medawar's paradigm (Chaouat, 2010,  
1642 2016; Moffett & Loke, 2004, 2006; Mor et al., 2011; Stadtmayer & Wagner, 2020b; Yoshizawa  
1643 2016). Moffett & Loke (2006) caution against conceptualizing embryos as analogs of allografts.  
1644 To my knowledge, this perspective has yet to reach the evolutionary literature on squamate  
1645 parity mode evolution (Foster et al., 2020; Graham et al., 2011; Gao et al., 2019; Murphy &  
1646 Thompson, 2011; van Dyke, Brandley, & Thompson, 2014; Murphy, Thompson, & Belov, 2009;  
1647 Recknagel et al., 2021a). Importantly, challenges to Medawar's paradigm do not preclude  
1648 immunological responses to viviparity. They simply suggest that the immune environment of the  
1649 uterus is uniquely evolved to support exposure to foreign tissue.

1650 The uterine immune system has a distinct evolutionary history from the periphery. It enables  
1651 cooperative dynamics with foreign tissues. It supports fertilization and early embryonic  
1652 development. This should have started evolving, distinct from the periphery, since internal  
1653 fertilization first originated. To contextualize this, I discuss the changing landscape of  
1654 immunological research at the maternal-fetal interface and what it means in the context of  
1655 amniote parity mode evolution. Overall, I hope readers consider how the uterus evolved to  
1656 support internal gestation, and which model systems may be appropriate to investigate this.

1657 Most literature on maternal-fetal immune dynamics limits itself to mammals. Squamates may  
1658 serve as a better comparative model for understanding the evolution of the uterine immune  
1659 system. Active research on the peripheral reptilian immune system (Zimmerman et al., 2010,  
1660 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et al., 2017;  
1661 Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights on this.

1662

1663 *(1) Comparing amniote immune systems*

1664 Cellular components of the innate immune system are conserved across jawed vertebrates  
1665 (Uribe et al., 2011; Zimmerman et al., 2010). The general machinery of the adaptive immune  
1666 system is ancient despite divergences and convergences across all domains of life (Ghosh et al.,  
1667 2011; Morales et al., 2017; Müller et al., 2018; Rimer et al., 2014). Diversification of antigen  
1668 receptor genes likely occurred independently in a lineage-specific fashion (Boehm et al., 2018).  
1669 Compared to mammals, the avian immune system requires less antigen (Larsson et al., 1998).  
1670 Birds also have faster but shorter antibody responses, potentially due to their higher body  
1671 temperatures (Zimmerman, 2010).

1672 Reptiles have the same general components of the mammalian immune system (Zimmerman,  
1673 2020). However, the reptilian immune system may not fit neatly into the two arms of mammalian  
1674 immune systems—innate and adaptive (Zimmerman, 2010; 2020). Expanding upon this is  
1675 beyond the scope of this review, but it is worth considering in future evolutionary research.  
1676 Squamates may serve as a better comparative model for understanding the evolution of the  
1677 uterine immune system. Active research on the peripheral reptilian immune system (Zimmerman  
1678 et al., 2010, 2020) and uterine immune activity in squamates (Graham et al., 2011; Hendrawan et  
1679 al., 2017; Murphy et al., 2009; Paulesu et al. 1995, 2008, 2005) will support future insights. I  
1680 refer readers to articles by Zimmerman et al. (2010, 2020) and Ghorai et al. (2018), and the book  
1681 by Williams (2012) for more information on the avian immune system.

1682

### 1683 (2) *Medawar's paradigm*

1684 Tolerance toward the foreign fetus was postulated to occur through immunological inertness,  
1685 immunosuppression or immunotolerance mechanisms (Medawar, 1953). Theoretically,  
1686 immunotolerance could be established if there are relatively small quantities of alloantigens

1687 present, resulting in regulatory responses rather than activating responses (Pradeu, 2011).  
1688 Contradicting this, the larger the alloantigen difference between the mother and embryo the  
1689 bigger and healthier the placenta is in rats (Chaouat et al., 2010). In humans, divergent HLA  
1690 profiles between mother and embryo do not lead to detrimental immune responses (Tilburgs,  
1691 Scherjon, & Claas, 2010). Instead, cooperative inflammatory responses between maternal and  
1692 fetal tissues support reproduction (Stadtmauer et al., 2020a). In humans, microchimeric cell  
1693 populations, presence of cells from one individual in another genetically distinct individual, are  
1694 now considered a normal expectation of pregnancy (Nelson, 2012).

1695 In his 1991 Nobel Lecture, Medawar acknowledged that maternal and embryonic tissues  
1696 have regular exposure to alloantigens (Medawar, 1991). It has become clear that the maternal  
1697 immune system actively responds to fetal alloantigen rather than responding solely with  
1698 ignorance or anergy (Arck & Hecher, 2013). Neither maternal immunosuppression/privilege nor  
1699 embryonic inertness/immaturity fully explain immune dynamics during gestation in mammals,  
1700 including those with the simple epitheliochorial placentation (Chaouat et al., 2010; Chavan,  
1701 Griffith & Wagner, 2017; Moffett & Loke, 2004, 2006; Stadtmauer & Wagner, 2020a).

1702

### 1703 *(3) Perspectives on the evolution of the uterine immune system*

1704 Viviparous reproduction existed eons before the origin of mammals and, to my knowledge,  
1705 no evidence suggests there was immune conflict within these taxa (Chaouat, 2016). Placentrophy  
1706 existed as far back as the invertebrate clade Bryozoa (Ostrovsky, 2013; Schwaha et al., 2019),  
1707 suggesting an ancient history for supportive maternal-fetal immune dynamics. Differing from  
1708 Medawar's paradigm, Polly Matzinger, who proposed the 'danger model' for the immune system

1709 (Matzinger, 2007), wrote “Reproduction cannot be a danger. It does not make evolutionary  
1710 sense” (Chaouat, 2016).

1711 In mammals, immunological cells at the maternal-fetal interface may not function through  
1712 self-non-self-discrimination, as they are understood to function in the rest of the body (Chaouat,  
1713 2016; Moffett & Loke 2004, 2006). The ‘maternal-fetal interface’ may be better conceptualized  
1714 as ‘maternal-fetal intra-action’ given the dynamics between maternal and fetal immune systems  
1715 in mammals (Yoshizawa, 2016). It is unclear if these insights apply to other viviparous amniotes.

1716 In mammals, immune factors in the uterus and placenta appear to be specifically evolved to  
1717 support maternal-fetal immune dynamics. Several cell types have unique functions and/or  
1718 phenotypes in utero—uterine NK (uNK) cells, uterine macrophages, uterine T regulatory cells  
1719 (Faas & de Vos, 2017; Mold et al., 2008, 2010; Mold & McCune, 2011). An immunosuppressive  
1720 antigen, HLA-G, is almost exclusively expressed by trophoblasts (Faulk & Temple, 1976;  
1721 Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al., 1997). Taken from an  
1722 evolutionary perspective, this suggests that the uterine immune system in viviparous mammals  
1723 evolved unique responses to allogenic tissues that differ from the periphery. Whether the  
1724 evolution of this system predates mammals remains to be explored, to my knowledge.

1725 It is suggested that viviparous reproduction is immunologically compatible in species with  
1726 less active adaptive immune system, like sharks (Chaouat, 2016). In these clades, innate immune  
1727 cells, like uNK cells, may be sufficient to regulate immune responses during pregnancy (Moffett  
1728 & Loke, 2004; Chaouat, 2016). Given that there is an unclear distinction between the innate and  
1729 adaptive immune system in reptiles (Zimmerman, 2020), determining immunological difficulty  
1730 of evolving viviparity in squamates requires further investigation.

1731 In uterine tissue of oviparous and viviparous skinks maternal antigens are expressed prior to  
1732 and during gestation and gravidity (Murphy et al., 2009), but the viviparous species in the study  
1733 have a unique expression profile of MHC antigens which may ‘hide’ the embryo from the  
1734 maternal immune system (Murphy et al., 2009). Similarly, in a reproductively bimodal skink,  
1735 *Saiphos equalis*, both oviparous and viviparous gestation is associated with expression of MHC  
1736 genes (Foster et al., 2020). Regardless of parity mode, *S. equalis* expresses genes associated with  
1737 immunocompetence, including MHC genes including *H2-EA* (Foster et al., 2020). The similar  
1738 profile between the oviparous and viviparous state is attributed to the use of very long egg  
1739 retention utilized by oviparous *S. equalis* (Foster et al., 2020). This highlights that extended  
1740 embryonic retention is accompanied with immunological responses in utero, which is relevant to  
1741 the EER model on amniote origins.

1742 Some of these genes expressed by *S. equalis* are also expressed in viviparous *Chalcides*  
1743 *ocellatus* during gestation including complement component genes (C3, C9) and MHC genes  
1744 (Brandley et al., 2012; Foster et al., 2020). The majority of immune genes expressed during  
1745 gestation/gravidity in *S. equalis* have immunoglobulin receptor binding functions (Foster et al.,  
1746 2020), an important feature of eutherian pregnancy that prevents rejection of the fetus through  
1747 actions of the maternal innate immune system (Alijotas-Reig, Llurba, Gris, 2014)). In another  
1748 reproductively bimodal skink, *Zootoca vivipara*, immune system response genes are enriched in  
1749 the set of genes under divergent selection in oviparous and viviparous genomes (Recknagel et al.,  
1750 2021a).

1751

1752 (4) *Implications of the reptilian immune system and morphology on parity mode evolution*



1753 Ectothermic reptiles may inherently have a more tolerogenic uterine environment compared  
1754 to mammals due to their slower antibody response. It can take up to six weeks to reach peak  
1755 concentrations (Ingram & Molyneux, 1983; Grey, 1963; Marchalonis et al., 1969; Pye et al.,  
1756 2001; Origgi et al., 2001; Work et al., 2000). A slower metabolism also makes several reptiles  
1757 more tolerogenic to pathogens (Ghorai & Priyam, 2018).

1758 During pregnancy in the viviparous skink, *Chalcides ocellatus*, there is a reduced response to  
1759 in vitro exposure to mitogens concanavalin A (Con A), phytohemagglutinin (PHA), and  
1760 *Escherichia coli* lipopolysaccharide (LPS) (Saad & El Deeb, 1990). Oviparous lizards exhibit  
1761 immune activation tradeoffs during reproductive cycles (Cox, Peadar, & Cox, 2015; Durso &  
1762 French, 2018; French, Johnston, & Moore, 2007; Uller, Isaksson, & Olsson, 2006).

1763 In the majority of viviparous squamates, the eggshell membrane is absorbed during  
1764 pregnancy (Blackburn, 1993). In mammals, epitheliochorial placentation (the most superficial  
1765 and non-invasive placenta type) is sufficient to cause immunorecognition from the mother.  
1766 Specialized placental cells, trophoblasts, may be more common in other viviparous vertebrates  
1767 than previously recognized (Blackburn, 2015a). For example, a gene with fusogenic properties  
1768 characteristics of trophoblast syncytins was recently identified in the *Mabuya* lizard placenta  
1769 (Cornelis et al, 2017). In mammals, trophoblasts are antigen presenting and actively participate  
1770 in maternal-fetal immune dynamics.

1771 A few viviparous squamates have placentas with characteristics similar to placentas found in  
1772 eutherian mammals—syncytialized cells layers, specialized zones such as areolae and  
1773 placentomes, or cellular invasion of maternal tissues by the fetus (Blackburn & Flemming, 2012;  
1774 Jerez & Ramírez-Pinilla, 2001; Vieira et al., 2007). The increased contact here may require more

1775 tightly regulated immune dynamics at the maternal-fetal interface compared to other viviparous  
1776 squamates.

1777

1778 (5) *The inflammation paradox*

1779 In mammals, implantation evolved from an ancestral inflammatory attachment reaction  
1780 (Griffith, Chavan et al., 2017). Inflammation is the most crucial system to support implantation,  
1781 but it is also the greatest threat to the continuation of pregnancy (Chavan et al., 2017). This  
1782 phenomenon is called the inflammation paradox. In humans, immune cells including uterine  
1783 macrophages, T cells of multiple subtypes, uterine natural killer (uNK) cells, dendritic cells, and  
1784 natural killer T (NKT) cells increase until implantation and remain abundant in the uterus  
1785 throughout first trimester (Bulmer et al., 1991; Bulmer, Williams & Lash, 2010). Early  
1786 implantation in humans is characterized by high pro-inflammatory T helper (Th)-1 cells and  
1787 cytokines (IL-6, IL-8, and TNF $\alpha$ ) (Yoshinaga, 2008). The exploitation of inflammatory  
1788 mechanisms for eutherian implantation and the shift toward non-inflammatory activity to  
1789 maintain pregnancy may have been key in enabling extended embryonic retention of eutherians  
1790 (Griffith, Chavan et al., 2017).

1791 How the inflammation paradox applies to viviparous squamates is unclear, given that  
1792 placentation in squamates and mammals is not homologous (Griffith, Van Dyke, & Thompson,  
1793 2013). In extrauterine pregnancies of mammals with non-invasive placentas, the embryo will  
1794 invade extrauterine tissue because it is not inhibited by uterine secretions (Vogel, 2005; Samuel  
1795 & Perry, 1972). However, in *Pseudemoia entrecasteauxii*, a viviparous skink that also has a non-  
1796 invasive placenta, extrauterine pregnancy does not result in invasive implantation of extrauterine  
1797 tissues (Griffith, Van Dyke, & Thompson, 2013). The inherent invasive nature of mammalian

1798 embryos outside of the uterus, compared to the non-invasive nature of viviparous squamate  
1799 embryos studied thus far, suggests that the parent-offspring conflict and the inflammation  
1800 paradox may be less pronounced in viviparous squamates compared to viviparous mammals.

1801

1802 *(6) Inertness and barriers at the maternal-fetal interface*

1803 The uterine environment is not inert or sterile (Agostinis et al., 2019; Erlebacher, 2013;  
1804 Moffett & Loke, 2006; Munoz-Suano, Hamilton, & Betz, 2011; Murphy, Thompson, & Belov,  
1805 2009; Yoshimura, Okamoto, & Tamura, 1997). In humans, the decidual layer of the uterus  
1806 during pregnancy is comprised of ~40% leukocytes (Ander, Diamond, & Coyne, 2019; Manaster  
1807 & Mandelboim, 2010). This cellular subpopulation has 70% uNK cells, 10-20% antigen  
1808 presenting cells (APCs) including macrophages and dendritic cells, and 3-10% T cells of several  
1809 subtypes (Abrahams et al., 2004; Hanna et al., 2006; Kämmerer et al., 2006; Le Bouteiller &  
1810 Piccinni, 2008; Liu et al., 2017; Manaster & Mandelboim, 2010; Moffett-King, 2002; Moffett &  
1811 Loke, 2006; Roussev et al., 2008). There is an abundance of decidual large granular lymphocytes  
1812 (LGLs), CD3-NK cells and CD3+ activated cytotoxic T cells, in the human uterus, that have  
1813 cytotoxic properties and produce cytokines, and these are affected by fetal MHC molecules  
1814 (Rieger, 2002).

1815 Birds also have immunocompetent cells in their oviducts. T and B cells are present in  
1816 chicken ovary where they are stimulated by estrogen (Barua & Yoshimura, 1999; Withanage et  
1817 al., 2003; Zettergren & Cutlan, 1992). Other immunocompetent cells in the chicken oviduct  
1818 include IgG+, IgA+ and CD3+ (Yoshimura, Okamoto, & Tamura, 1997). Immune competent  
1819 cells located throughout the mucosal tissue of avian oviductal segments including macrophages,

1820 antigen presenting cells (APCs) expressing MHC class II antigens, helper T cells and cytotoxic T  
1821 cells, and premature B cells (Das, Isobe, & Yoshimura, 2008).

1822 Inert barriers between maternal and fetal tissues may 'hide' the embryo. In oviparous taxa,  
1823 the eggshell may serve as a barrier. However, the antimicrobial properties of the eggshell matrix  
1824 in birds demonstrate that even the eggshell is not inert. The FAS ligand, also called APO-1 or  
1825 CD95, in humans and rodent embryonic tissue was proposed to serve as a barrier because it  
1826 causes apoptosis of surrounding maternal immune cells (Kayisli et al., 2003; Makrigiannakis et  
1827 al., 2008).

1828 Medawar suggested that an impermeable placenta strictly regulates molecular exchanges,  
1829 preventing rejection of the embryo (Medawar, 1991). Syncytiotrophoblasts lack cellular junctions  
1830 and thus it was postulated to serve as this barrier (Ander et al., 2019). However, the growing data  
1831 on bidirectional cellular traffic of APCs, even in mammals with noninvasive placentas, rejected  
1832 this hypothesis (Bakkour et al., 2014; Burlingham & Bracamonte-Baran, 2015; Fujiki et al.,  
1833 2008; Turin et al., 2007).

1834

### 1835 *(7) T cell populations and mammalian viviparity*

1836 In mammals, immune-dynamics at the maternal-fetal interface are established through  
1837 innate and adaptive immune responses. There is a delicate balance between ratios of Th1, Th2,  
1838 Th17, Tregs and memory T cells at the maternal-fetal interface in eutherian mammals during  
1839 gestation (Chaouat et al., 1997; Kieffer et al., 2019; Peck & Mellins, 2010; Saito et al., 2010; Wu  
1840 et al., 2014). A shift in utero from T helper type 1 (Th1) cells to T helper type 2 (Th2) cells  
1841 during gestation in mammals equates to a shift from pro-inflammation to anti-inflammation. The  
1842 galectin proteins, GAL-13 and GAL-14, expressed by syncytiotrophoblasts, bind to T cells

1843 where they inhibit activation, induce apoptosis, and enhance interleukin-8 (IL-8) production  
1844 (Balogh et al., 2019).

1845 Growing research is revealing the central role of Tregs at the maternal-fetal interface  
1846 during pregnancy in mammals (Teles et al., 2013; Wienke et al., 2019). Tregs play a central role  
1847 in immunosuppression in mammals (Attias, Al-Aubodah, & Piccirillo, 2019). Differentiation of  
1848 Tregs is governed by the transcription factor, *FOXP3* (Ramsdell & Rudensky, 2020).

1849 Alloantigen-dependent, uterine T cell signaling, and immunocompetent embryonic cells and their  
1850 products facilitate enhanced regulatory phenotypes of immune cells overall (Ander et al., 2019).

1851 The T-cell dependent adaptive immune system of mammals is unique. This may have  
1852 prompted their intricate balance of Treg mediators of immunotolerance at the maternal-fetal  
1853 interface (Chaouat, 2016). Birds rely more heavily on B cells. In non-avian reptiles, T helper  
1854 cells are functional, but the presence and function of other T cell subsets is unclear (Zimmerman,  
1855 2020; Zimmerman, Vogel, & Bowden, 2010). The potential role of T cells and Tregs in  
1856 viviparous squamate gestation should not be discounted. Treg-like cells have been identified in a  
1857 pufferfish, *Tetraodon nigroviridis* (Wen et al., 2011), suggesting that Tregs may have an ancient  
1858 evolutionary history.

1859

#### 1860 (8) Progesterone, cytokines, and maternal-fetal immune dynamics

1861 In addition to the role of progesterone in uterine quiescence (embryonic retention) and  
1862 hepatic vitellogenesis (nutrient provisioning), it also plays a role in maternal-fetal immune  
1863 dynamics. In the uterus of pregnant mammals, progesterone concentrations are associated with  
1864 altered B cell immunoglobulin secretion, inhibition of NK-cell mediated cytotoxicity and the shift  
1865 from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) dominated immune responses

1866 (Druckmann & Druckmann, 2005). Progesterone is also associated with immunomodulatory  
1867 effects (Ortega Brown et al., 1990). During gestation in *Agkistrodon piscivorus*, a viviparous pit  
1868 viper, progesterone concentrations are associated with decreased complement performance  
1869 (Graham et al., 2011), a portion of the immune system that promotes inflammation, among other  
1870 immune functions.

1871 In humans, progesterone induced protein (PIBF) is transported by placental extravillous  
1872 trophoblasts to maternal lymphocytes causing the induction of interleukin-10 (IL-10) production,  
1873 contributing to the Th2 dominant responses (Szekeres-Bartho, Šučurović, & Mulac-Jeričević,  
1874 2018). IL-10 is a potent anti-inflammatory cytokine that is produced by multiple cell types  
1875 (Zimmerman, Bowden, & Vogel, 2014). It is associated with Th2 response, and it inhibits Th1  
1876 responses. The phenotype of uterine macrophages is affected by trophoblasts when they secrete  
1877 IL-10 and macrophage colony-stimulating factor (M-CSF) (Svensson-Arvelund et al., 2021). IL-  
1878 10 inhibits IFN- $\gamma$  and increases in response to infection in chickens (Giansanti, Giardi, & Botti,  
1879 2006; Rothwell et al. 2004). In the uterus of the oviparous skink, *Lampropholis guichenoti*,  
1880 during gravidity and non-gravidity, IL-10 is expressed (Griffith et al., 2016).

1881 Proinflammatory cytokines may be downregulated during reproductive periods to limit  
1882 maladaptive immune responses to the foreign fetus (Zimmerman, Vogel, & Bowden, 2010). In  
1883 mammals, IL-1 allows release of hormones in human trophoblasts (Petraglia et al., 1990;  
1884 Masuhiro et al., 1990; Yagel et al., 1989), facilitates implantation (Haimovici, Hill, & Anderson,  
1885 1991; Hill, 1992; Tartakovsky & Ben-Yair, 1991), and influences the initiation of labor (Romero  
1886 et al., 1989, 1992). Regulation of the proinflammatory cytokines tumor necrosis factor (TNF)  
1887 and interleukin 1B (IL-1 $\beta$ ) is of particular importance in eutherian pregnancy (Haider & Knöflner,  
1888 2009; Paulesu, Romagnoli, & Bigliardi, 2005; Saito et al., 2010; Tayade et al., 2006).

1889 The uterine tissue of two reproductively bimodal squamates—viviparous individuals of  
1890 *Chalcides chalcides*, and oviparous and viviparous individuals of *Zootoca vivipara*—express IL-  
1891 1 $\beta$  (Paulesu et al., 1995, 2005; Romagnoli et al., 2003). In the uterus of the viviparous skink,  
1892 *Pseudemoia entrecasteauxii*, during gestation regulation of TNF and IL-1 $\beta$  at the transcriptional  
1893 and post-translation levels, respectively, may reduce inflammation (Hendrawan et al., 2017). The  
1894 pro-inflammatory function of IL-1 $\beta$  in *Pseudemoia entrecasteauxii* may play a role developing a  
1895 more complex placenta (Hendrawan et al., 2017). The placenta of *Chalcides chalcides* expresses  
1896 pro-inflammatory cytokines, IL-1 $\alpha$  and IL-1 $\beta$ , at specific times during gestation (Paulesu et al.,  
1897 1995). During gestation, *Chalcides ocellatus* also differentially expresses 27 other interleukins  
1898 and interleukin related products (Brandley et al., 2012).

1899 The expression of IL-34 in a marsupial, the fat-tailed dunnart, during pre-implantation  
1900 (Whittington et al., 2018) may have an immunosuppressive function to help tolerate potential  
1901 contact of maternal and fetal tissues when the embryonic shell coat disintegrates (Lindau et al.,  
1902 2015). In chickens, IL-34 regulates Th1 and Th17 cytokine production (Truong et al., 2018).  
1903 During gestation in *Pseudemoia entrecasteauxii*, IL-16 and IL-1 $\alpha$  are expressed in addition to  
1904 three receptors for Th17 family cytokines—IL-17RA, IL-17RC, and IL-17RA (Griffith,  
1905 Brandley, et al., 2016, 2017). In the yolk sac of *Pseudemoia entrecasteauxii* during pregnancy  
1906 interleukin related molecules, *ILDR1*, *IRAK1*, and *SIGIRR*, are differentially expressed (Griffith  
1907 et al., 2016). This profile suggests the presence of tricellular tight junctions and/or tricellulin  
1908 (Higashi et al., 2013; Ikenouchi et al., 2005), and regulation of toll-like receptors (TLRs) and/or  
1909 IL-1R signaling (Kawagoe et al., 2008; Lin, Lo, & Wu, 2010; Muzio et al., 1997).

1910

1911 (9) *The major histocompatibility complex and maternal-fetal immune dynamics*

1912 A substantial amount of literature on maternal-fetal immune dynamics was focuses on uNK  
1913 cells. Uterine NK cells have a distinct phenotype and function from peripheral NK cells. They  
1914 have several activating receptors (Manaster & Mandelboim, 2010) but do not exert cytolytic  
1915 functions on embryonic trophoblasts that they are in contact with (King, Birkby, & Loke, 1989).  
1916 Allorecognition of embryonic placental cells by uNK cells is a key regulator of the maternal-fetal  
1917 immune mechanisms that support placentation in mammals (Moffett & Colucci, 2014). When  
1918 cells lose their ability to express any HLAs, uNK cells are shown to kill them (Hunt et al., 2005;  
1919 Ishitani et al., 2003; King, Allen et al., 2000).

1920 In humans, expression of the classical MHC class I (C-MHCI) molecule HLA-C, and  
1921 nonclassical MHC class I (NC-MHCI) molecules HLA-E, HLA-F and HLA-G on trophoblasts  
1922 inhibit uNK cell-mediated cytotoxicity (Hunt et al., 2003; King, Burrows et al., 2000). Differing  
1923 from this, mismatched HLA-C profiles trigger rejection of the transplanted organs (Petersdorf et  
1924 al., 2014). Selection for balanced polymorphisms in HLA-C alleles and their killer  
1925 immunoglobulin receptors (KIRs) is proposed to be driven by reproductive success, rather than  
1926 immune recognition of pathogens (Trowsdale & Betz, 2006). Dimorphisms of HLA-C emerged  
1927 recently within primates (Adams & Parham, 2001).

1928 Similar patterns in MHC profiles have been explored in other viviparous amniotes. C-MHCI  
1929 antigen, H2-K, is expressed on giant trophoblast cells of mice and this is attributed to  
1930 trophoblast-induced uterine vasculature transformation (Arcellana-Panlilio & Schultz, 1994;  
1931 Chatterjee-Hasrouni & Lala, 1982; Hedley et al., 1989; King et al., 1987; Sellens, Jenkinson, &  
1932 Billington, 1978). H2-D antigen is co-expressed with H2-K in virtually all their other nucleated  
1933 cells (Madeja et al., 2011). However, H2-K expressing trophoblasts lack H2-D expression. This



1934 parallels the expression patterns of C-MHC molecules at the maternal-fetal interface in humans  
1935 and may be an evolutionarily conserved pattern (Madeja et al., 2011).

1936 In humans, NC-MHCI molecule, HLA-G, is especially tolerogenic (Carosella et al., 2015;  
1937 González et al., 2012; Hviid et al., 2004; Kovats et al., 1990). In adults, HLA-G is almost  
1938 exclusively expressed by fetal trophoblasts compared to adult cells (Faulk & Temple, 1976;  
1939 King, Burrows et al., 2000; Kovats et al., 1990; Rajagopalan & Long, 2012; Rouas-Freiss et al.,  
1940 1997). It supports immunotolerance at the maternal-fetal interface (Rebmann et al., 2014). The  
1941 role of HLA-G in supporting tolerogenic responses to organ transplants appears to be an  
1942 exploitation of its role in immunotolerance in the utero during pregnancy (Rebmann et al., 2014).  
1943 HLA-G is upregulated by several molecules that serve essential roles during gestation including  
1944 progesterone (Yie, Xiao, & Librach, 2006; Yie et al., 2006), IFN- $\alpha$ , IFN- $\beta$ , and IFN- $\gamma$  (Rebmann  
1945 et al. 2003; Lefebvre et al., 2001; Ugurel et al., 2001; Yang, Geraghty, & Hunt, 1995), and IL-10  
1946 and TGF- $\beta$  (Cadet et al., 1995; Moreau et al., 1999).

1947 A similar NC-MHCI gene to HLA-G exists in horses (Davies et al., 2006) where it likely  
1948 functions to protect the embryo from NK-cell mediated attack (Ott et al., 2014). NC-MHC  
1949 molecules with similar structure to HLA-G are also found in Rhesus monkeys (Boyson et al.,  
1950 1997) and baboons (Stern et al. 1987). Mice have two NC-MHCI genes that are expressed on the  
1951 surface of their placentas and on pre-implanted embryos (Sipes et al., 1996).

1952 In the gestating uterus of the viviparous skink, *Pseudemoia entrecasteauxii*, four putative C-  
1953 MHCI and two putative NC-MHCI molecules are expressed (Murphy, Thompson, & Belov,  
1954 2009). This pattern resembles the C-MHCI and NC-MHCI expression profiles of mammals,  
1955 suggesting that this viviparous skink utilizes a similar physiological mechanism to 'hide' the  
1956 embryo (Murphy, Thompson, & Belov, 2009). One of the putative NC-MHCI genes (Psen-

1957 160Ut/Psen-78G) has a substitution at position 150 where a tryptophan is substituted for a  
1958 leucine (Murphy, Thompson, & Belov, 2009). When Psen-160Ut/Psen-78G was aligned to NC-  
1959 MHC I genes of vertebrates ranging from fish to eutherian mammals, tryptophan was conserved  
1960 at position 150 except in Psen-160Ut/Psen-78G and HLA-G (Murphy, Thompson, & Belov,  
1961 2009). Whether this reflects an evolutionary history associated with immune tolerance at the  
1962 maternal-fetal interface in *Pseudemoia entrecasteauxii* requires further investigation.

1963 MHC I genes are also expressed in reproductive tissues of oviparous skinks (*Ctenotus*  
1964 *taeniolatus* and *Lampropholis guichenoti*) during non-reproductive periods and during late  
1965 gravidity (Murphy, Thompson, & Belov, 2009). A similar pattern is found in viviparous skinks  
1966 *Eulamprus tympanum*, *Niveoscincus metallicus*, *Pseudemoia entrecasteauxii* and the  
1967 reproductively bimodal skink *Saiphos equalis* which all express MHC I genes at non-  
1968 reproductive periods and during late pregnancy/gravidity (Murphy, Thompson, & Belov, 2009).  
1969 MHC gene H2-EA is also expressed during gestation with long egg retention in *Saiphos equalis*.

1970 The butyrophilin subfamily 1 member A (*BTN1A1*) is located in the MHC I region of the  
1971 genome in mammals (Trowsdale, 2011). *BTN1A1* is differentially expressed in the uterus during  
1972 gestation in a viviparous lizard, *Chalcides ocellatus* (Brandley et al., 2012). *BTN1A1* may have  
1973 important antimicrobial properties in chicken eggshells (Mann, Maček, & Olsen, 2006). In  
1974 mammals *BTN1A1* is the major protein associated with fat droplets in milk (Jeong et al., 2009).

1975

1976 (10) *Microchimerism and maternal-fetal immune dynamics*

1977 Billingham, Brent and Medawar suggested the concept of actively acquired immunologic  
1978 tolerance during pregnancy 70 years ago (Billingham, Brent, & Medawar, 1953; Ribatti, 2015).  
1979 Subsequent research over the following decades revealed that substantial transfer of proteins,

1980 parasites and even immunologically active cells occurs between mother and embryo (Adams &  
1981 Nelson, 2004; Axiak-Bechtel et al., 2013; Bakkour et al., 2014; Burlingham, 2010; Fujiki et al.,  
1982 2008; Gitlin et al., 1965; Khosrotehrani et al., 2005; Owen, 1945; Turin et al., 2007).  
1983 Microchimerism, where there is <0.1% donor chimeras in host tissue, is relatively pervasive  
1984 among eutherians during pregnancy. It plays a role in establishing tolerance to non-inherited  
1985 antigens. For example, cell populations from the mother that are transferred into embryonic  
1986 lymph nodes enable the establishment of embryonic Tregs that are tolerogenic toward non-  
1987 inherited maternal antigens (Mold et al., 2008).

1988       Microchimeric cellular populations are transferred across all placental types (Axiak-Bechtel  
1989 et al., 2013; Bakkour et al., 2014; Fujiki et al., 2008; Khosrotehrani et al., 2005; Turin et al.,  
1990 2007). Fetal and maternal cells persist for decades after birth across a range of tissues in mother  
1991 and offspring, respectively (Adams & Nelson, 2004; Bakkour et al., 2014; Bayes-Genis et al.,  
1992 2005; Bianchi et al., 1996; Evans et al., 1999; Jonsson et al., 2008; Stevens et al., 2004). There is  
1993 even a call in the immunology literature to shift from the conventional paradigm of “self vs  
1994 other” to instead consider the “self” as inherently chimeric (Nelson, 2012). Given that  
1995 epitheliochorial placentation is sufficient to illicit microchimeric cell populations, the occurrence  
1996 of similar bidirectional cellular traffic is a reasonable possibility in viviparous squamates.

1997

1998       (11)       *Paternal alloantigens*

1999       Under tenants gleaned from transplant medicine, the maternal immune system would illicit  
2000 an attack response as early as insemination when maternal tissues are exposed to paternal  
2001 alloantigens (Borziak et al., 2016; Schumacher & Zenclussen, 2015; Seavey & Mosmann, 2006).  
2002 Instead, maternal cells immunologically recognize them at this time without attack (Schumacher

2003 & Zenclussen, 2015; Seavey & Mosmann, 2006; Zenclussen et al., 2010). Treg expansion, a  
2004 process with major influence on maternal-fetal immunotolerance in mammals, is proposed to be  
2005 driven by several different factors found in seminal plasma (Baratelli et al., 2005; Teles et al.,  
2006 2013). Mothers may maintain fetal-specific Tregs with memory of the paternal alloantigens  
2007 (Zenclussen et al., 2010), expediting Treg response in future pregnancies with the same father  
2008 (Rowe et al., 2012).

2009 Alloantigen exposure at the time of insemination is not restricted to mammals. Seminal fluid  
2010 of chickens contains two MHC I paternal alloantigens and one MHC II alloantigen (Borziak et  
2011 al., 2016). It also contains proteins involved in immunity and antimicrobial defenses (Borziak et  
2012 al., 2016). In hens, evidence suggests that a protective local immunity to pathogens is established  
2013 after exposure to semen but the mechanisms for this remain unclear (Reiber & Conner, 1995;  
2014 Reiber, Conner, & Bilgili, 1995).

2015 In mammals, paternal alloantigens and cytokines in seminal fluid drive immune tolerance  
2016 (Schjenken & Robertson, 2014). Mammalian seminal plasma contains immune-factors (Kelly,  
2017 1995; Schjenken & Robertson, 2014)—TGF- $\beta$  (Breuss et al., 1993; Chu & Kawinski, 1998;  
2018 Slater & Murphy, 1999), IL-8 (Gutsche et al., 2003), and soluble IL-2 receptor (Srivastava,  
2019 Lippes, & Srivastava, 1996), prostaglandin E2 (PGE2) and 19-hydroxyprostaglandin E (19-  
2020 hydroxy PGE) (Denison et al., 1999), soluble tumor necrosis factor (TNF) receptors (Liabakk et  
2021 al., 1993), receptors for the Fc portion of  $\gamma$ -globulin, spermine (Evans, Lee, & Flugelman, 1995),  
2022 and complement inhibitors (Kelly, 1995). In horses and pigs, respectively, the proteins CRISP3  
2023 (Doty et al., 2011), PSP-I and PSP-II (Rodriguez-Martinez et al., 2010), act as signaling agents  
2024 in seminal fluid.

2025 Secretions of growth factors, cytokines and chemokines from cervical and endometrial  
2026 tissues immediately following insemination generates a proinflammatory environment that likely  
2027 aids in implantation. In the utero-vaginal junction of chickens and the utero-tubal junction of  
2028 pigs, expression of several genes were shared following mating compared to non-mating and  
2029 these genes were involved with immune-modulation (*IFIT5*, *IFI16*, *MMP27*, *ADAMTS3*, *MMP3*,  
2030 *MMP12*) and pH-regulation (*SLC16A2*, *SLC4A9*, *SLC13A1*, *SLC35F1*, *ATP8B3*, *ATP13A3*), a  
2031 process essential for implantation (Atikuzzaman et al., 2017, 2015). Instead of mounting an  
2032 attack, it appears that the uterine immune system and paternal genes work cooperatively to  
2033 support pregnancy in mammals and gravidity in birds. Whether this applies to reptiles, and how  
2034 it may influence immune dynamics involved with squamate parity mode evolution, deserves  
2035 investigation.

2036

2037 (12) *Discussion and future directions—maternal-fetal immune dynamics & the*  
2038 *evolution of parity modes*

2039 Immune processes appear to be important for both oviparity and viviparity—as evidenced  
2040 here, in part, by overlapping expression profiles of immune genes in female reproductive tissues  
2041 of chickens and pigs, expression of paternal antigens in avian seminal fluid, and uterine  
2042 expression of maternal antigens in oviparous and viviparous skinks. This highlights the scientific  
2043 advances made since Medawar’s paradigm, when embryos were treated as analogs to allografts.  
2044 Nonetheless, viviparity is associated with complex immune dynamics between maternal, fetal,  
2045 and paternal tissues.

2046 Overall, evolving appropriate immunological responses is one hurdle of transitions to  
2047 viviparity in squamates. This is evidenced by the unique MHC expression profiles identified in

2048 some viviparous skinks compared to oviparous relatives (Murphy et al., 2009); and the detection  
2049 of divergent selection in immune response genes in viviparous and oviparous *Zootoca vivipara*  
2050 (Recknagel et al., 2021a). Labile parity modes in squamates may be supported if they are more  
2051 heavily reliant on the innate immune system for reproduction. However, reptiles may not have  
2052 distinguished innate and adaptive immune systems (Zimmerman et al., 2020).

2053 Changes to genes that serve overlapping functions across the Main Five may have a  
2054 disproportionate influence on transitions between parity modes. In this section I reviewed two  
2055 molecules, *TGF-β* and progesterone, that exert influence on multiple Main Five categories.  
2056 Progesterone influences uterine quiescence (embryonic retention), hepatic vitellogenesis  
2057 (nutrient provisioning) and regulation of inflammatory responses in utero (maternal-fetal  
2058 immune dynamics). Genes in the *TGF-β* family play a role in placental development and  
2059 maternal-fetal immune dynamics. *TGF-β* family is implicated in placental development in  
2060 eutherians (Hempstock et al., 2004; Caniggia et al., 2000; Lafontaine et al., 2011). A *TGF-β*  
2061 receptor protein (*TGFBR1*) was associated with placental development in *Phrynocephalus*  
2062 *vlangalii* (Gao et al., 2019). In humans *TGF-β* upregulates tolerogenic HLA-G in utero and is an  
2063 immune factor in mammalian seminal fluid. Multiple genes in the *TGF-β* family are also  
2064 differentially expressed during gestation in other viviparous lizards, *Pseudemoia entrecasteauxii*  
2065 and *Saiphos equalis* (Foster et al., 2020; Griffith et al., 2016). Examining the functions of *TGF-β*  
2066 and progesterone across other amniotes may reveal insights into how these molecules influence  
2067 the evolution of parity modes.

2068 In mammals, inflammation appears to be involved with two of the Main Five processes—  
2069 regulation of maternal-fetal immune dynamics and embryonic retention. It is intriguing to  
2070 consider the implications this has for the interconnectedness of the Main Five. Greater

2071 interconnectedness would suggest that changes to few genes involved with the Main Five could  
2072 cause a cascading effect to support more labile transitions between parity modes.

2073       Implantation and parturition in therian mammals evolved from a shared inflammatory  
2074 attachment reaction (Hansen et al., 2017). The process of implantation has important  
2075 implications for maternal-fetal exchanges of inorganic and organic material and maternal-fetal  
2076 immune dynamics. Given that inflammation is associated with implantation and parturition  
2077 implicates it in gas, water, and nutrient provisioning (including calcium here), maternal-fetal  
2078 immune dynamics and length of embryonic retention. However, implantation in mammals and  
2079 viviparous squamates is not homologous (Griffith, Van Dyke, & Thompson, 2013). Therefore, it  
2080 is difficult to make inferences about how substantial the influence of inflammation is on the  
2081 evolution of parity modes in squamates. Nonetheless, the abundant literature on uterine  
2082 inflammatory processes during human pregnancy and the evolution of inflammatory processes  
2083 that supported the evolution of viviparity in mammals (Challis et al., 2009; Chavan, Griffith, &  
2084 Wagner, 2017; Mor et al., 2011; Griffith, Chavan et al., 2017; Stadtmauer & Wagner, 2020a)  
2085 serve as indispensable resources for exploring the role of inflammation in squamate viviparity. I  
2086 resist expanding on this further. I suspect that the immune system plays a central role in dictating  
2087 the plasticity of parity modes. However, further work is necessary to validate this.

2088

2089

## 2090       **VII. Conclusions**

2091

2092       (1) Through holistic consideration of the unique complexity of parity mode evolution, within  
2093       the context of genomic and transcriptomic studies across interdisciplinary fields, this

2094 review provided a new perspective on the history of parity mode transitions in amniotes  
2095 and squamates. The overlapping activity of immune genes in utero, genes for calcium  
2096 transport, placentation, and hormonal regulation across mammals, birds, and reptiles hint  
2097 at discoveries to be made. There is a fascinating history to the evolutionary physiology  
2098 and genomics of reproduction in amniotes that is ripe for downstream research.

2099 (2) Changes to gene(s) or physiological processes associated with more than one of the Main  
2100 Five should disproportionately influence parity mode evolution—*SLC* gene superfamily,  
2101 TGF- $\beta$ , *BMPRI1B*, progesterone, *PMCA*, calbindin-D28K, *SPP1*, sustained functioning of  
2102 the corpora lutea and inflammation, and the genes associated with both gestation length  
2103 and eggshell traits in *Zootoca vivipara* (Recknagel et al., 2021a).

2104 (3) Growing evidence in the medical literature suggests that immune system interactions at  
2105 the maternal-fetal interface in mammals did not evolve simply through immunotolerance,  
2106 evasion, immunosuppression, or immunological barriers (Chaouat, 2016; Chavan,  
2107 Griffith, & Wagner, 2017; Moffett & Loke, 2004, 2006). Instead, maternal-fetal immune  
2108 dynamics have a deep evolutionary history that enables both embryo and mother to  
2109 interact cooperatively (Yoshizawa, 2016). Viviparity and extended embryonic retention  
2110 are assuredly associated with immunological responses across amniotes, including  
2111 squamates (e.g. Foster et al., 2020). Oviparous birds and squamates are also known to  
2112 differentially express genes during gravidity, with one exception to my knowledge,  
2113 *Lampropholis guichenoti* (Griffith et al., 2016).

2114 (4) Compared to viviparous endothermic amniotes, ectothermy likely influences parity mode  
2115 evolution differently because it entails slower antibody responses and a greater reliance  
2116 on climatic conditions for embryonic development. This and the Cold Climate



2117 Hypothesis are likely relevant to the origin of the amniotic egg and squamate parity mode  
2118 evolution. Climatic shifts during the origin of amniotes should be explored for their  
2119 consistency with the EER model.

2120 (5) Two new mechanisms for transitions between oviparity and viviparity, without  
2121 necessitating intermediate stages, stand out from the cumulative research on the Main  
2122 Five. These are presented here (Conclusions 6 and 7) as tools to be broadened and  
2123 challenged with the goal of advancing scientific insight on the subject.

2124 (6) The genomics and physiology of amniote parity mode evolution does not preclude an  
2125 origin of viviparity in the MRCA of Lepidosauria. I propose the following mechanism—a  
2126 change to the phenotype or function of mammillary knobs occurred in the MRCA of  
2127 Lepidosauria, instantaneously preventing calcium carbonate deposition (basal cap  
2128 hypothesis); the eggshell loss enabled uterine exposure to chorioallantoic progesterone  
2129 production (extending embryonic retention) and incipient calcium matrotrophy  
2130 (supporting embryonic development); parturition occurred via 1) placental progesterone  
2131 withdrawal or 2) overdistension of the uterus triggers contractions. This is one way to  
2132 imagine viviparity evolving in the MRCA of Lepidosauria.

2133 a. Hypothesis testing: If the genes that code for the KS-proteoglycan, “mammillan”,  
2134 that makes up mammillary knobs are absent or non-functional across squamates  
2135 and tuatara, then this would support the basal cap hypothesis. To test this  
2136 hypothesis, the genes must be identified in Archelosaur genomes and proteomes.  
2137 Additionally, ancestral state reconstructions on the eggshell and eggshell  
2138 membrane should be generated across oviparous and viviparous Archelosaurs,  
2139 utilizing current recommendations for characterizing eggshell microstructure

2140 (Legendre et al., 2022). This will require also developing a system to accurately  
2141 characterize eggshell membranes.

2142 (7) As discussed, the calcium secreting capacity of the uterus is maintained in oviparous and  
2143 viviparous squamates. Nonetheless, a reversal back to oviparity may evolve most easily  
2144 within viviparous clades with matrotrophic calcium provisioning through the following  
2145 sequence of events—calcium secretions in utero stick to the eggshell membrane instead  
2146 of being absorbed by the chorioallantois; oviposition can then occur early in embryonic  
2147 development in one of two ways 1) the death of corpora lutea or 2) the calcified eggshell  
2148 blocks a threshold of chorioallantoic progesterone production from reaching uterine  
2149 tissue; the calcified eggshell provides embryonic calcium that is transported upon  
2150 embryonic metabolic demand.

2151 a. Hypothesis testing: Recent reversals should have physiological or genomic  
2152 remnants of a viviparous past. Given that viviparous squamates generally have  
2153 more active uterine immune systems to support gestation, oviparous reversals  
2154 should 1) have more immune genes expressed in utero than ancestrally oviparous  
2155 squamates, and 2) these immune genes should have stronger signatures of relaxed  
2156 selection than immune genes expressed in a close relative during viviparous  
2157 gestation.

2158 (8) If the scientific community agrees to utilize squamates as a model for studying the  
2159 evolutionary genomics of parity modes in amniotes, then consider the following—1)  
2160 oviparous *Z. vivipara* and *P. przewalskii*, differentially express many genes during  
2161 gravidity and these were associated with eggshell traits and stage of eggshell gland  
2162 development, respectively (Gao et al., 2019; Foster et al., 2022); 2) Only two or zero

2163 genes are differentially expressed during gravidity in *Lerista bougainvillii*, and  
2164 *Lampropholis guichenoti*, respectively (Griffith et al., 2016). 3) This suggests that  
2165 embryonic retention until the limb bud phase, common to squamates, does not necessarily  
2166 require regulatory changes in an oviparous uterus. If we extrapolate this to stem  
2167 amniotes, it implies there is a route wherein an oviparous egg can be retained for an  
2168 extended period of time without an immunological problem. The EER model is the most  
2169 realistic explanation for the origin of the amniote egg. If we accept this, then all  
2170 oviparous squamates that differentially express a substantial number of genes during  
2171 gravidity can be conceptualized as reversals.

2172 (9) If we accept point eight as a possibility, then *Saiphos equalis* and *Zootoca vivipara* may  
2173 represent reproductively bimodal species (RBS) that transitioned in the reverse, viviparity  
2174 back to oviparity; and RBS *Lerista bougainvillii* may represent a species that transitioned  
2175 in the forward, from oviparity to viviparity. Future work can test this by applying point  
2176 7.A in this conclusion.

2177 (10) The lack of differential gene expression in *Lampropholis guichenoti* during gravidity  
2178 fits neatly into Medawar's Paradigm, one of the biology's most influential and impactful  
2179 theories. *L. guichenoti* achieves a gravid state with immunological barriers (e.g. the  
2180 eggshell?) and/or inertness (e.g. no immune DEGs). Future work should look at  
2181 differentially expressed genes across stages of gravidity in the species to explore this  
2182 further.

2183 (11) Given that the mammillary layer is described as unique to Archelosaurs, the original  
2184 amniote egg may not have had a mammillary layer. Instead, it makes logical sense that  
2185 the original amniote egg became ensheathed in an eggshell membrane, followed by

2186 calcium deposition that looks comparable to what we see in squamates. We can test this  
2187 by using the framework of the basal cap hypothesis, described briefly in point 6 of this  
2188 conclusion and at length in section III.3.

2189  
2190

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2196       **IX.   References**

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