

1 Title:

2 Greater loss of female embryos during human pregnancy: A novel mechanism.

3

4 Subtitle:

5 Maternal tissues “interview” embryos during implantation, with female candidates disadvantaged by their
6 greater genetic, metabolic, and hormonal distinctiveness

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30 **Summary**

31 Given an equal sex ratio at conception, we can only explain the excess of human males at birth by greater
32 loss of females during pregnancy. I propose that the bias against females during human development is the
33 result of a greater degree of genetic and metabolic “differentness” between female embryos and maternal
34 tissues than for similarly aged males, and that successful implantation and placentation represents a threshold
35 dichotomy, where the acceptance threshold shifts depending on maternal condition, especially stress. Right
36 and left ovaries are not equal, and neither are the eggs and follicular fluid that they produce, and I further
37 hypothesise that during times of stress, the implantation threshold is shifted sufficiently to favour survival of
38 females, most likely those originating from the right ovary, and that this, rather than simply a greater loss of
39 males, explains at least some of the variability in the human sex ratio at birth.

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59 Introduction

60 The choosy uterus

61 Pregnancy is a conflict between mother and offspring.^[1] Selection acts on maternal genes to limit the supply
62 of resources to developing offspring so as to maximise (or at least stabilise) maternal fitness, whereas fetal
63 genes are selected to maximise growth.^{[1], [2]} These selfish offspring may seek to maximise their own growth
64 at the expense of future offspring, whereas mothers should favour equal investment in all present and future
65 offspring.^[3] Imprinting of maternal genes therefore serves to limit the growth and/or function of the placenta.
66 There is also conflict between maternal and paternal alleles, as fathers have an interest in improved survival
67 of (their) current offspring even at the expense of future offspring, which may have a different father. With
68 respect to offspring sex ratios, the Trivers and Willard Hypothesis proposes that as females deviate from the
69 “average” condition they should bias the production of one sex over the other, driven by improved likelihood
70 of producing grandchildren,^[4] and logic suggests that this sex ratio manipulation should occur as early as
71 possible to minimise wasted maternal investment. Since implantation represents the first major instance of
72 fetal-maternal conflict, I hypothesise that it is at this point that a large component of variation in the human
73 sex ratio arises, facilitated by endometrial sensing of embryo quality,^{[5]–[8]} most specifically the degree of
74 “*differentness*” from the mother. Implantation therefore represents a threshold dichotomy,^[9] where passing
75 the threshold results in successful implantation (and at least a chance of further development) and failing
76 results in loss, but where the threshold itself can vary within and between women.

77 The mammalian implantation process is thought to have evolved from endometrial inflammation – a natural
78 reaction of maternal tissues to a foreign body.^{[10], [11]} Whilst the initial stages of implantation are pro-
79 inflammatory, post-implantation embryonic development requires an anti-inflammatory endometrial state,
80 and there must therefore be a point of acceptance by the maternal tissues at or around this time.^[6] The first
81 few weeks of gestation place relatively little demand upon the mother and therefore involve little maternal
82 investment, and so embryo quality control should occur early, with the fetal-maternal interface (i.e. the
83 interaction between fetal ligands and maternal receptors) representing the front line in the battle between
84 invading trophoblast and defending maternal tissues. Indeed, discussion of early fetal-maternal interactions is
85 full of references to trophoblast “invasion” of the endometrium, and the literature is full of war-like
86 references to “fighting lines”,^[12] “no man’s land”,^[13] and the embryo as a “deceitful and treacherous
87 enemy”.^[14] A more appropriate comparison for the very earliest stages of implantation at or soon after the

88 initiation of embryo-maternal contact may be an interview, where the embryo seeks to make a favourable
89 impression.^[13] The evolution of deeper implantation in placental mammals facilitated more thorough vetting
90 of offspring, and these deeper forms of implantation may have evolved to reduce the “ease” by which a
91 mother may reject an embryos through sloughing of superficial layers of endometrium.^[13] This process,
92 together with rapid evolution of placental proteins^[3] reflects the fetal-maternal arms race. How might this
93 maternal vetting of embryos occur, and why might it preferentially target female embryos to result in a male-
94 biased sex ratio at birth?

95 Male and female embryos differ from the very point of conception. Only males can express genes on the Y
96 chromosome, and, prior to the completion of X chromosome inactivation, females can produce up to twice
97 the amount of gene product for any gene encoded by the X chromosome. Male and female embryos therefore
98 express different genes even at very early stages, varying from around 600 differentially-expressed genes in
99 mouse blastocysts,^[15] to up to a third (2,921) of expressed transcripts in cow.^[16] Male embryos grow
100 faster,^{[17], [18]} and so a female embryo will be ready for implantation later than an identically-aged male, and
101 is more likely to miss the implantation window when the endometrium is most receptive (a period of around
102 4 days, typically 6-8 days post-ovulation^[19]).

103 Male and female embryos are also metabolically distinct, as females are thought to make more use of the
104 pentose phosphate pathway, possibly because of an additional copy of the X-linked *G6PDI* gene,^[18]
105 although others have cast doubt on this idea.^[20] Metabolism is likely the most fundamental difference
106 between early male and female embryos, and certainly one of the most dynamic,^[21] and metabolically “quiet”
107 embryos may survive better than more active ones.^{[22]–[24]} In this “quiet embryo hypothesis”, metabolic
108 signatures of the embryo are assumed to reflect viability, for instance levels of DNA damage,^[23] with
109 maternal selection against metabolically-active (putatively less viable) embryos. Of course, this quest for
110 quietness, if taken too far, would ultimately result in embryonic death, and so there must be a window of
111 viability within which successful embryos must operate. Accepting that the endometrium acts as a biosensor
112 to reject “unsuitable” embryos,^{[5]–[7]} and that there may be a “Goldilocks zone” of embryonic potential,^[25]
113 females may be discriminated against from the very earliest stages of their development as early female
114 embryos may be more different to their mother than their male counterparts. Although males have Y
115 chromosome-specific genes that the mother does not herself possess, the X chromosome encodes more genes
116 (846 to the 63 on the Y chromosome in Ensembl release GRCh38.p12), and prior to completion of X

117 chromosome inactivation differential gene expression is therefore greater in females. Genes on sex
118 chromosomes are known to regulate autosomal genes,^[20] and the greater number of X-linked genes in
119 females will have a concomitantly larger effect on the number of downstream autosomal genes that are up-
120 or down-regulated. Male and female embryos are both genetically distinct from their mother (i.e. encode
121 paternally-derived genes), but again, because of the size of the X chromosome, females have a greater
122 amount of paternal DNA (the X is 156Mb long, the Y just 57Mb, which may have relevance for the extent of
123 imprinting), and a greater number of paternal genes.

124 A comprehensive study of the human sex ratio from conception to birth^[26] shows an initial large loss of male
125 embryos in the first week or so, followed by a longer period of female-biased loss in the first trimester. As a
126 result, the cohort sex ratio is male-biased from the end of the first trimester, and remains this way until the
127 last few weeks of pregnancy, where male-biased stillbirth^[27] likely comes into play. The greatest number of
128 female losses therefore occurs at or soon after implantation, and in the following weeks as placentation
129 progresses. It is here that maternal-fetal contact is both established and, through placentation, extended, to
130 reach the closest possible juxtaposition of maternal and fetal tissues and blood supplies, and this period also
131 represents one of relatively limited fetal growth and maternal investment. It is no surprise that this should
132 represent the “interview” period. Even once the interview is passed, the endometrium may still present a
133 more hostile environment to female embryos, which may go some way to explaining sex differences in the
134 male and female placenta, where female placentae are more sensitive to perturbation in the peri-conception
135 period, and show reduced growth and a greater amount of variation in placental gene and protein
136 expression.^{[28], [29]}

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138 What is the extent of sex-biased loss in human pregnancy?

139 Whilst 10% of clinically-recognised pregnancies end in miscarriage, the true number is estimated to be much
140 higher as many pregnancies are lost before they are identified, and up to one third of all pregnancies may end
141 in spontaneous abortion (miscarriage).^{[30]-[34]} However, far higher values have been proposed.^{[35], [36]} In 1975,
142 Roberts and Lowe attempted to predict the annual number of conceptions in England and Wales in 1971,^[37]
143 and suggested that up to 78% of conceptions were “lost” (unaccounted for in live birth and still birth
144 records). Their analysis was based only on married women, hypothesised a mean frequency of coitus twice a
145 week (one in four of which was unprotected), and did not include data for pregnancies ending in elective or

146 therapeutic abortion. Using data from the National Surveys of Sexual Attitudes and Lifestyles (Natsal)^[38] it is
147 possible to refine these calculations somewhat, and these updated calculations suggest that the assumption
148 that around a third of all conceptions might be lost is valid (Box 1, Table 1).

149 In England and Wales, all live births and stillbirths must be registered, and there is extensive historical data
150 available on numbers of live births and stillbirths, including sex ratios (it should be noted however that in
151 October 1992, the Stillbirth (Definition) Act 1992 changed the gestation cut-off for stillbirths from 28 or
152 more weeks of gestation to 24 or more weeks, and so data from 1993 onwards is not comparable to previous
153 years). In addition to extensive live birth and stillbirth data, the requirement that all practitioners in England
154 and Wales who perform therapeutic or elective abortions must notify the Chief Medical Officer means that
155 abortion statistics (including number of abortions by gestation week) are available going back to the late
156 1960's. The stability of the overall sex ratio at birth (Figure 1) suggests that, in England and Wales at least,
157 there is no sex-selective abortion, and the general increase in the number of legal abortions, and the lack of
158 maternal deaths due to complications of illegal abortions^[39] also suggests that there are few if any unrecorded
159 abortions. In England and Wales between 1993 and 2017 there were 16,489,289 maternities (a pregnancy
160 resulting in the birth of one or more children including stillbirths, of which around 1.5% resulted in multiple
161 births); 16,656,203 live births (8,114,739 female and 8,541,464 male, with on average 1,053 males born per
162 1,000 females); 86,714 stillbirths (41,059 female and 45,655 male, with on average 1,112 males stillborn per
163 1,000 females); 4,512,024 legal elective and therapeutic abortions, and 28,269,072 conceptions (assuming
164 that 33% of conceptions result in spontaneous abortion (miscarriage) and that the recorded live birth,
165 stillbirth and abortion figures therefore represent 67% of total conceptions). Historically, the male bias at
166 birth was taken to result from the production of a greater proportion of males at conception, although more
167 recent data from *in vitro* fertilisation supports a balanced sex ratio at conception (see Orzack et al.^[26] for
168 discussion), as does the simple mechanics of equal segregation of X and Y chromosomes during
169 spermatogenesis. We can therefore reasonably conclude that the 28,269,072 conceptions comprised equal
170 numbers of males and females. If males and females were also equally represented in the therapeutic and
171 elective abortion dataset (i.e. the abortus sex ratio is 50:50), then 2,256,012 males and 2,256,012 females
172 were aborted. However, more recent work^[26] supports a slightly female-biased cohort sex ratio during early
173 pregnancy based on chorionic villus sampling, amniocentesis and induced abortions, and a conservative
174 estimate of a 55:45 female:male sex ratio ≤ 12 weeks and 45:55 female:male ≥ 13 weeks might be more

175 appropriate. In the study period, 4,044,380 therapeutic and elective abortions occurred ≤ 12 weeks of
176 gestation and 467,644 occurred ≥ 13 weeks, with 2,435,740 girls aborted to 2,076,284 boys, for an average of
177 853 boys aborted per 1,000 girls (Figure 2, Supplemental table S1). Using these data, it is possible to deduce
178 that 28,269,072 conceptions resulted in 7,014,131 spontaneous abortions (miscarriages) in England and
179 Wales between 1993 and 2017, with on average 141,720 females and 138,845 boys lost each year, for an
180 average sex ratio of 980 boys per 1000 girls (Supplemental table S2). Significantly more girls are lost during
181 pregnancy ($P < 0.00001$, Pearson's χ^2 test).

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183 Stress, miscarriage, and variation in the sex ratio at birth

184 The human sex ratio at birth is not stable, and, in England and Wales between 1993-2017, ranged from 1,047
185 boys per 1,000 girls to 1,057 boys per 1,000 girls. The predicted miscarriage sex ratio over the same period
186 ranged from 956 boys per 1,000 girls in 1993 to almost parity (999 boys per 1,000 girls) in 2006 (Figure 3).
187 The variation seen in 2006 follows the July 7th 2015 terror attacks in London, and reflects the general
188 observation that sex ratio varies following stressful events, and that parental hormone levels around
189 conception in some ways influence the sex ratio of their offspring.^{[40]-[46]} Why might stress impact the human
190 sex ratio at birth, and what exactly is changing?

191 The human stress response is mediated by the hypothalamic-pituitary-adrenal axis, and ultimately results in
192 the release of glucocorticoid hormones (primarily cortisol) by the adrenal cortex. Interestingly, this process
193 also results in release of progesterone by the adrenal cortex, and leads to increased circulating levels of
194 progesterone in serum,^[47] most likely because progesterone and cortisol are both cholesterol derivatives, and
195 progesterone is a precursor in the synthesis of cortisol. Similarly, both testosterone and estradiol are
196 cholesterol-derivatives, and so production of these hormones may also increase during the stress response.
197 The link between cholesterol, hormones, and changes to the sex ratio at birth are hinted at in differences in
198 ABO blood group cholesterol levels and sex ratios,^[48] and the link between cortisol and progesterone may
199 also explain some seasonal variations in the human sex ratio at birth, as cortisol levels are known to vary
200 throughout the year.^[49] If one of the factors involved in setting the threshold of acceptance for embryo
201 implantation and peri-conception survival is the degree of differentness from the mother, then changes to
202 hormone levels in the maternal circulation might alter the acceptance threshold, so embryos that previously
203 would have been lost are now able to implant and survive. In particular, those female embryos produced

204 from eggs originating in the right ovary, which would normally be rejected as too different might now
205 survive in greater numbers.

206

207 Ovarian asymmetry

208 Humans demonstrate directional asymmetry, most obviously in the positioning of internal organs such as the
209 heart, stomach and intestines.^[50] These asymmetries can ultimately be traced to determination of left-right
210 axes during embryogenesis, dictated by left-biased ciliary flow and an ancient gene regulatory network
211 involving *PITX2*, *NODAL* and *LEFTY*. Asymmetric *PITX2* expression is maintained and plays a role in
212 subsequent organ development, and, in birds, underlies asymmetric development of the gonads, reaching its
213 most extreme manifestation in the single (left) ovary and oviduct of many species.^{[51]–[53]} Among mammals,
214 functional asymmetry of left and right ovaries has been reported from many species, including mice,^[54]
215 shrews,^[55] gerbils,^[56] viscachia,^{[57], [58]} bats,^[59] and waterbuck^[60]. Although human gonadal asymmetry is
216 perhaps most apparent in males, where the right testis is larger, the inherent directional asymmetry of
217 vertebrate embryos demonstrates that the human left and right ovary are not equal from the earliest stages of
218 development. In adults, this asymmetry manifests itself in anatomical relations (the left ovary lies adjacent to
219 the sigmoid colon, the right nearer the appendix), venous drainage (the left ovary drains into the left renal
220 vein, the right into the inferior vena cava^{[61], [62]}), and function. The right ovary may ovulate more frequently
221 and favour pregnancy,^{[63]–[67]} and this elevated function possibly leaves the right ovary more susceptible to
222 ovarian cancer,^{[68], [69]} cystic ovarian endometriosis,^[70] and ruptured corpus luteum.^{[61], [71]–[73]} Ectopic
223 pregnancy may also be more common on the right,^{[74]–[76]} and gonadal tissues are unevenly distributed in true
224 hermaphrodites, with ovaries more common on the left, and testes/ovotestes more common on the right.^{[77]–}
225 ^[79] The data on functional asymmetry of human ovaries and possible differential susceptibility to disease are
226 noisy with generally small effects, however, the consistent trends, coupled with developmental and
227 anatomical asymmetries, tells us that we should not consider left and right ovaries as equals.

228 What implications might ovarian asymmetry have for human reproduction? There are hints in the literature
229 that the right ovary might ovulate more, and favour pregnancy,^{[63]–[67]} but one possibility that is generally
230 neglected is that differences between left and right ovaries might lead to variation in the human sex ratio at
231 birth. It has long been recognised that more males are born than females in many populations, despite greater
232 susceptibility of boys to stillbirth,^[27] (Figure 1). Whilst the sex ratio at birth is typically stable, and for the

233 most part biased towards males, there is variation across populations, only some of which is likely due to
234 sex-specific elective abortion.^[80] The remaining variation can seemingly be explained by demography, with
235 those of African origin having lower sex ratios^{[81], [82]} (even becoming female-biased in some cases^[81]),
236 latitude,^[83] and seasonality.^{[84]–[86]} Perhaps most interestingly, the sex ratio at birth can be perturbed by
237 stressful events, such as the 1995 Kobe earthquake;^[87] famine;^[88] war;^{[89]–[91]} terrorist attacks;^{[92]–[94]} historic
238 royal events;^[95] the Superbowl;^[96] and economic stress.^{[97], [98]} Such seasonal variation, coupled with the
239 effects of stress, is evidence for hormonal influences on the human sex ratio at birth, and, indeed, it has
240 previously been suggested that hormonal concentrations in parents around conception can alter sex ratios.^{[41],}
241 ^[99] Once asymmetry of left and right ovaries is accepted, these influences may become easier to explain. The
242 right and left ovaries differ in their venous drainage, and as a result, pressure in the right ovarian vein is
243 higher than the left.^{[61], [62]} The right ovary therefore drains more slowly than the left, and so we can expect
244 hormones to accumulate differentially, resulting in higher concentrations of estradiol, testosterone,
245 progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and cortisol on this side. These
246 elevated concentrations are maintained, and perhaps boosted, by counter current exchange between ovarian
247 veins and arteries.^[100] Prior to ovulation, a human oocyte is bathed in approximately 5ml of follicular fluid,
248 containing estradiol and progesterone in concentrations roughly 500x and 1000x higher respectively than in
249 serum,^{[101]–[103]} and the freedom of steroid hormones to move across membranes means that the oocyte will
250 equilibrate to follicular fluid conditions prior to ovulation. Oocytes from the right and left ovaries will
251 therefore experience different environments as folliculogenesis progresses, with levels of estradiol,
252 progesterone and others far in excess of maternal serum levels, and they will carry these hormones with them
253 in their cytoplasm (and that of their companion cells) as they are released. At the same time, several
254 millilitres of asymmetric follicular fluid is released, producing different microenvironments in the left and
255 right fallopian tubes as the egg begins its journey towards fertilisation.

256

257 Ovarian asymmetry and human reproduction

258 Human sperm are attracted to follicular fluid.^{[104]–[106]} More specifically, a subset of sperm cells undergo
259 capacitation, and as a result demonstrate chemotaxis,^[107] with low levels of progesterone known to act as a
260 chemoattractant.^{[108]–[110]} There is some debate regarding the role that follicular fluid plays *in vivo*, with
261 evidence from animal studies suggesting $\leq 1\%$ of the follicular fluid released along with the egg actually

262 enters the fallopian tube,^{[111]-[114]} equating to $\leq 50\mu\text{l}$ in humans. Others have suggested that follicular fluid is
263 the major fluid constituent in fallopian tubes immediately post-ovulation, as the egg is carried into the tube
264 via a wave of fluid.^[115] Follicular fluid that does not directly enter the fallopian tube is released into the
265 peritoneal cavity immediately adjacent to the ovary, and the ruptured follicle may continue to secrete
266 follicular fluid for a short time following ovulation (the corpus luteum may also secrete hormones into the
267 peritoneal cavity for a period *prior* to ovulation^[116]). There is therefore a pool of hormone-enriched fluid
268 adjacent to the fimbria before and after ovulation, and this may be drawn into the tube by ciliary flow^{[117], [118]}
269 or enter adjacent blood vessels. Since the composition of fallopian tube fluid differs between left and right
270 sides, and since sperm respond to progesterone concentrations in the picomolar range,^{[107], [119]} these
271 differences may have implications for sperm chemotaxis. Given that the follicular microenvironment is
272 virtually saturated with progesterone, the oocyte and its associated cumulus cells are likely equilibrated to
273 follicular fluid conditions, and the oocyte-cumulus complex itself is also a source of chemoattractants,
274 including progesterone.^{[114], [119], [120]} We therefore have a situation where the chemoattractant concentrations
275 within oocyte-cumulus complexes differs between left and right sides, and where the fallopian tube fluid that
276 bathes these complexes also differs.

277 With this in mind, there are several ways that ovarian asymmetry (as demonstrated by variation in hormonal
278 concentrations in follicular fluid from left and right ovaries) might influence human fertility. Firstly,
279 progesterone can inhibit ciliary beating in the fallopian tube,^{[121], [122]} and so egg motility may differ between
280 the left and right tubes, with extended migration times reducing the possibility of “healthy” sperm reaching
281 the egg. Secondly, different hormone/chemoattractant concentrations on the left and right may affect sperm
282 chemotaxis, either positively, through improved or earlier attraction of sperm, or negatively, through
283 saturation of receptors. Saturated receptors can no longer detect increases in chemoattractant concentration,
284 rendering chemotaxis impossible, and studies of human sperm cell responses to progesterone have indeed
285 shown that high concentrations are ineffective, and that sperm more readily respond to concentrations in the
286 picomolar range.^{[107], [119]} These effects may operate over both long (from the sperm reservoir to the oocyte-
287 cumulus complex) or short (within the oocyte-cumulus complex) distances. Similarly, X and Y chromosome-
288 bearing sperm may respond differently to signals from the right and left. There has been much debate over
289 morphological or behavioural differences between X and Y chromosome-bearing sperm, with some
290 suggesting that those carrying the smaller Y chromosome may have a smaller head size and swim faster (and

291 potentially further) than those bearing the larger X chromosome.^{[123], [124]} The difference in DNA content
292 between X and Y chromosome-bearing sperm is roughly 3%, and, although small, it does seem likely that
293 this has at least some influence on size and/or shape of the sperm head.^{[18], [125]–[127]} Sperm carrying X or Y
294 chromosomes may therefore have either variable numbers of chemoreceptors such as CatSper^{[128], [129]} and
295 hOR17-4,^[130] or these receptors may be distributed differently across the sperm head. A higher number of
296 receptors on larger X chromosome-bearing sperm might improve sensitivity, whilst a lower number on those
297 carrying a Y may make them more easily saturated. Variability in receptor distribution across larger or
298 smaller sperm heads might also improve directionality, or simply improve sensitivity by widening the
299 detection window. Most importantly, the different intrinsic hormone concentrations of eggs originating in the
300 left and right ovaries might impact embryonic implantation, placentation, and post-implantation survival and
301 especially greater survival of female embryos during times of stress when the maternal acceptance threshold
302 shifts in their favour.

303 The literature concerning the human sex ratio at birth is very male-centric. Discussion of variation in sex
304 ratio, and especially declines, typically assumes that this is the result of a greater loss of males (the “fragile
305 male” idea^{[131]–[133]}), possibly because most male losses occur later in development, and so are more visible.
306 A similar result can of course also be explained by more females surviving than would usually be the case
307 ^[134]. Such increased survival can affect the sex ratio at birth in several ways, most obviously with a greater
308 number of female live births, but also by impacting subsequent pregnancies. In those actively trying to
309 conceive, a female embryo lost early (at or soon after implantation) might have been replaced by a male in a
310 subsequent cycle, but survival of the female embryo removes that mother from the pool of potential
311 reproducers for the duration of the pregnancy, and sometime beyond. Reproductive behaviour may also be
312 important, particularly in terms of stopping rules,^[135] where couples desiring a child of a specific sex stop
313 reproducing once this is achieved, or where couples might wish for a child of each sex, and continue
314 reproducing until this is achieved. In conditions which favour survival of females, those seeking a girl might
315 therefore stop reproducing after one pregnancy, and those who seek a boy and a girl would stop if they
316 already have a boy. Conversely, those seeking a boy who already have one girl might continue to reproduce
317 after having another, and, if the stressful conditions endure, may continue to have girls. However, it must be
318 kept in mind that changes to the human sex ratio at birth are typically small, varying only between a low of
319 51.02:48.98% male:female in 1927 to a high of 51.58:48.42% male:female in 1973, based on live birth data

320 for England and Wales from 1927-2017. In the 62,454,461 live births recorded during this period, only
321 1,685,618 more boys than girls were born. Whilst ovarian asymmetry and a threshold dichotomy of
322 implantation and placentation success predicated upon uterine biosensing may not account for all of this
323 variation, it does represent a novel mechanism by which we can explain existing data, such as the influence
324 of maternal hormones around the time of conception, and the impact of stressful events and seasonality on
325 the human sex ratio at birth.

326

327 Conclusions

328 Ovarian asymmetry is a neglected aspect of reproductive biology. It is rare to find a scientific publication
329 dealing with embryos produced by assisted reproductive technology or the composition of follicular fluid
330 that identifies from which ovary the study materials were sourced. Similarly, studies of implantation rarely,
331 if ever, identify the sex of embryos concerned. Research in adult humans, or using animals, is required to
332 report the participant sex, and it is perhaps time for greater awareness of embryonic sex and ovary-of-origin
333 in the study of early human development. A greater appreciation of ovarian asymmetry may also be
334 necessary for explaining variation within and between women. Similarly, consideration of testicular
335 asymmetry, and that of the uterus and fallopian tubes, may also be overdue, as early developmental
336 asymmetries likely impact all of these structures.

337 More girls are lost during pregnancy than boys, and as a result the human sex ratio at birth is biased towards
338 males. Male and female embryos are not equal from the very moment of conception, and it should be no
339 surprise that these differences might influence some of the most important aspects of mammalian
340 development, such as implantation and placentation. The greater genetic and metabolic “differentness” of
341 female embryos, at least prior to the development of functional gonads, may count against them in the
342 threshold dichotomy^[9] of acceptance or rejection by maternal tissues. Such discrimination may ultimately
343 work in their favour however, if it follows a pattern similar to that in ‘reverse’ imprinting,^{[136], [137]} where
344 expression of maternal alleles might be favoured if elevated gene expression increases the possibility of
345 spontaneous abortion, but leads to an increase in robustness (increased growth and pre- and post-natal
346 survival) of survivors. If losses occur early in pregnancy, minimal resources have been invested and cost to
347 the mother is limited. Boys exhibit greater infant mortality than girls^[138] (and higher stillbirth rates) and so it
348 may be that the greater loss of girls earlier in pregnancy actually explains their later robustness.

349

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353

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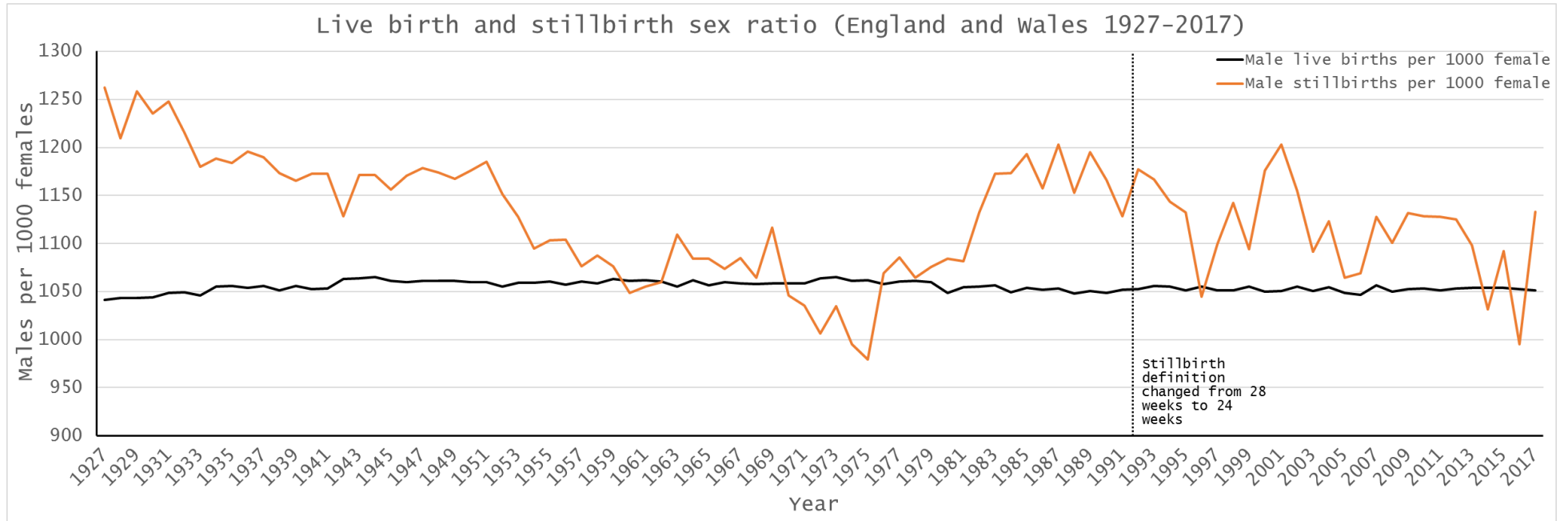


Figure 1. Live birth and stillbirth sex ratio in England and Wales, 1927-2017. On average 1,055 males were born per 1,000 females, and there are no years where more females are born than boys. The definition of stillbirth changed from 28 weeks of gestation to 24 weeks of gestation in 1992, and on average 1,133 boys were stillborn per 1,000 girls between 1927 and 1992, and 1,112 per 1,000 between 1993 and 2017. In the entire dataset, there are only three years where more girls were stillborn than boys (1974, 1975, 2016).

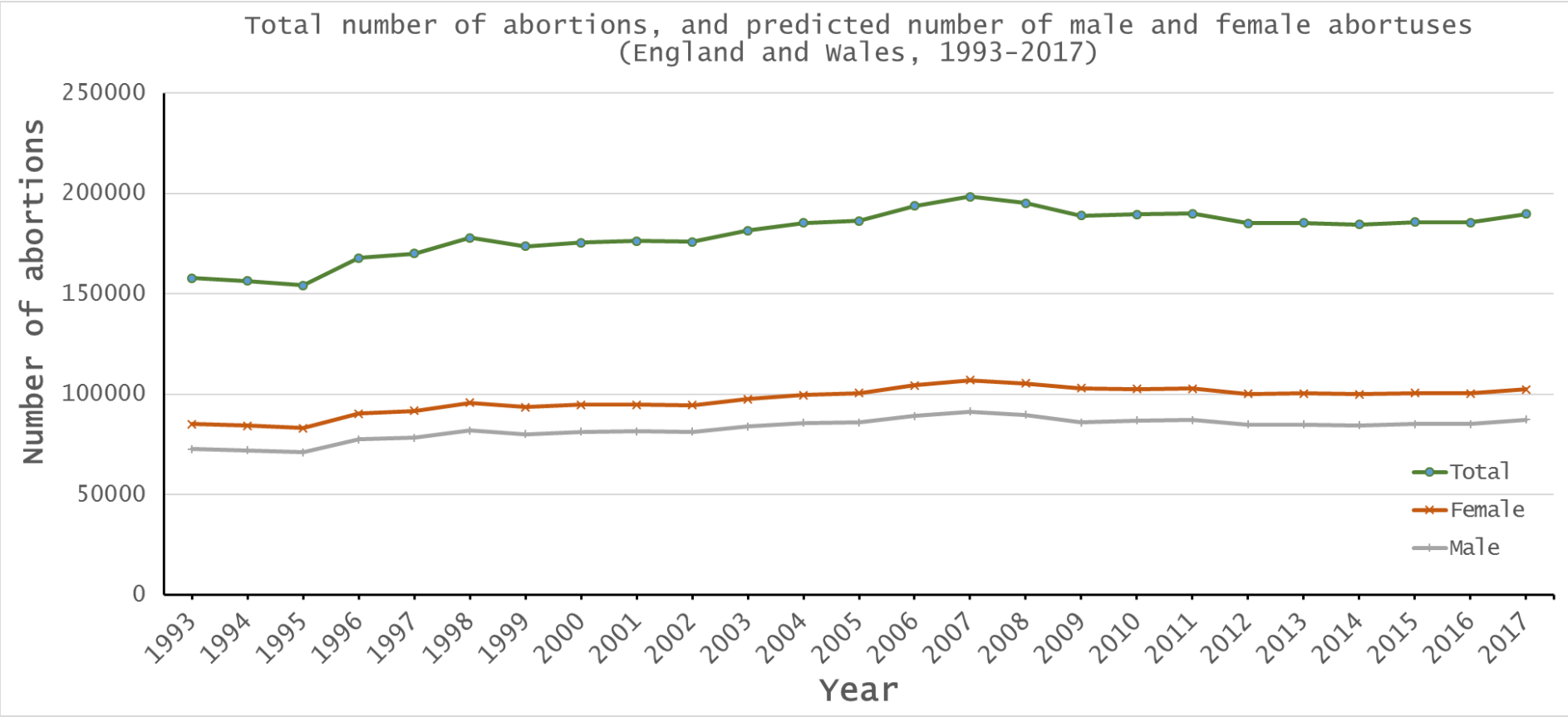


Figure 2. Sex ratio of therapeutic and elective abortions in England and Wales, 1993-2017, determined on the assumption that early (≤ 12 weeks) abortions are biased towards females (55:45) and later abortions (≥ 13 weeks) are biased towards males (45:55).

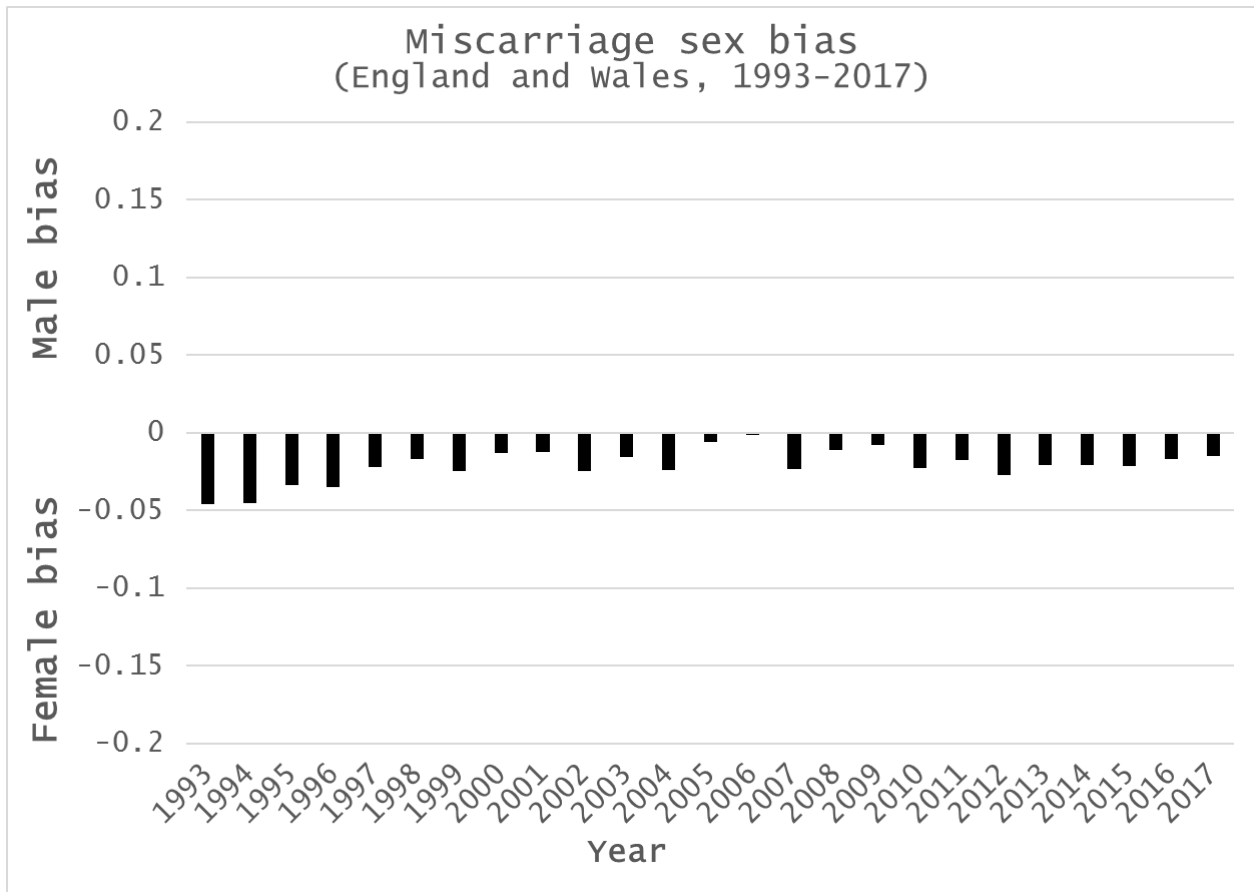


Figure 3. Relative miscarriage sex bias in England and Wales, 1993-2017, calculated as $1 - (\text{females miscarried} / \text{males miscarried})$, calculated if 33% of all conceptions result in miscarriage. A value of 0 indicates no bias, a positive value would show male bias, and a negative value a female bias. Miscarriages are biased towards females in every year of this 25 year dataset, with a marked decrease in the miscarriage sex ratio around 2005-2006, following the 7th July 2005 terrorist bombings in London, and a smaller dip in 2009 that may be due to the 2008 financial crisis.

Table 1. Theoretical prediction of the number of miscarried products of conception in England and Wales in 2012. Sexual habits are based on Natsal-3^[38] for women aged 16-44, and the remaining data are from ONS statistical datasets as described in the text. The predicted miscarriage rate is 43% overall, or 38% for women aged 20-39 (responsible for the majority of live births, stillbirths and abortions).

| | Age | | | | | |
|---|----------|----------|----------|----------|----------|-----------|
| | Under 20 | 20-24 | 25-29 | 30-34 | 35-39 | All |
| Number of women | 1362919 | 1893629 | 1925992 | 1898383 | 1803418 | 8884341 |
| Annual acts of vaginal sex (assuming 44 per woman per year) | 59968436 | 83319676 | 84743648 | 83528852 | 79350392 | 390911004 |
| Annual acts of unprotected vaginal sex (assuming one in six is unprotected) | 9994739 | 13886613 | 14123941 | 13921475 | 13225065 | 65151834 |
| Unprotected acts occurring within 48-hour period around ovulation (i.e. 1/14) | 713910 | 991901 | 1008853 | 994391 | 944648 | 4653702 |
| Assume one in three of these results in fertilisation | 237970 | 330634 | 336284 | 331464 | 314883 | 1551234 |
| Number of live births to these women | 33815 | 132456 | 202370 | 216242 | 114797 | 699680 |
| Number of stillbirths to these women | 217 | 669 | 936 | 912 | 601 | 3118 |
| Number of elective and therapeutic abortions to these women | 30539 | 54558 | 41882 | 30353 | 18523 | 145316 |
| Estimated loss | 173399 | 142951 | 91096 | 83957 | 180962 | 672364 |
| Percentage loss | 73% | 43% | 27% | 25% | 57% | 43% |

Box 1. Calculating the number of missing conceptions.

Natsal-3^[38] suggests that women aged 16-44 in the survey period (6th September 2010 – 31st August 2012) had on average 4.9 occasions of sexual intercourse (defined as vaginal, oral or anal intercourse) in the preceding 4 weeks, of which 69% included vaginal sex (defined as a man's penis in a woman's vagina). The frequency of sexual intercourse for this age group is likely nearer 1.2 occasions per week, with 0.85 instances of vaginal sex per week. The annual frequency (i.e. for 52 weeks) of vaginal sex for women aged 16-44 in the survey period was therefore 44.2, not the 104 previously used by Roberts and Lowe.^[37] The proportion of unprotected acts of coitus during the survey period is also lower than the 25% estimate of Roberts and Lowe, and is likely nearer 5-7% for women aged 16-44,^[139] increasing to around 10% if less effective methods of contraception are included, or to 1/6 if some consideration is given to those trying to conceive or who were already pregnant. The number of unprotected instances of vaginal sex per woman per year is therefore around 7, and, of these, 1/14 will occur within 48 hours of ovulation. Given a fertilisation rate of around 60% in *in vitro* fertilisation,^[140] where sperm quality and quantity is likely higher than that of a "normal" ejaculate at the point of fertilisation *in vivo*, a fertilisation rate of one in three seems reasonable. The Office for National Statistics mid-year population estimate for mid-2012 predicted that there were 8,884,341 women between the ages of 16-39 in England and Wales, and so the estimated the number of "missing" conceptions (i.e. those not accounted for in the relevant live birth, stillbirth, and legal therapeutic and elective abortion statistics) for women aged 16-39 in 2012 was 43%. For women aged 20-39 (responsible for 91% of all live births, 88% of stillbirths and 78% of abortions), the average rate of loss was 38% (Table 1). Given the inherent uncertainty in these calculations, an estimate that around a third of all conceptions are lost seems reasonable.

Supplemental information

Supplemental methods

Data for numbers of maternities, live births and stillbirths, including numbers of males and females, were collected from the Office for National Statistics (<https://www.ons.gov.uk/>) ‘Review of the Registrar General on births and patterns of family building in England and Wales’, Series FM1 (numbers 22-37, covering 1993-2008), the ‘Characteristics of Birth 2, England and Wales’ dataset (2009-2013), the ‘Birth characteristics dataset’ (2014-2016), and the ‘Summary of key birth statistics, 1838 to 2017’. Data on numbers of legal abortions from 2011-2017 were obtained from the Department of Health and Social Care (DHSC) ‘Abortion statistics, England and Wales’ collection (<https://www.gov.uk/government/collections/abortion-statistics-for-england-and-wales>), and for 1993-2010 from the UK Government Web Archive (<http://www.nationalarchives.gov.uk/webarchive/>). Numbers of stillbirths by age of mother for 2012 were obtained from the from the ‘Child Mortality Statistics 2012’ dataset (<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/childmortalitystatisticschildhoodinfantandperinatalchildhoodinfantandperinatalmortalityinenglandandwales>), and England and Wales population data were obtained from the ‘MYE2: Population Estimates by single year of age and sex for local authorities in the UK, mid-2012’ (<https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland>).

Gestation week data is variable across the abortion dataset, and so statistics were pooled into abortions occurring either ≤ 12 weeks or ≥ 13 weeks. A comprehensive study of the human sex ratio from conception to birth^[26] supports a female-biased cohort sex ratio during early pregnancy based on chorionic villus sampling, amniocentesis and induced abortions, and I have therefore chosen a conservative estimate of a 55:45 female:male sex ratio ≤ 12 weeks and 45:55 female:male ≥ 13 weeks. Using these values, I calculated the number of male and female abortuses each year.

Adding together the total number of live births, stillbirths and legal abortions provided the number of pregnancies, and accepting that these represent 67% of actual conceptions (i.e. the probability that a conception resulted in miscarriage was 33%) determined the relevant number of conceptions. If the primary sex ratio is equal, then equal numbers of males and females are conceived, and subtraction of the known

numbers of live and stillborn males and females, and the predicted male and female abortuses left the number of products of conception lost to miscarriage.

Statistical significance of deviation of calculated numbers of miscarried males and females from expected numbers (males and females are equally susceptible to miscarriage) was assessed using Pearson's χ^2 test. All calculations were rounded to the nearest whole number to reflect the impossibility of conceiving a fraction of a person, and so in some cases annual totals are not the sum of their constituent parts. It also goes without saying that the ratios presented here address only a narrow range of biological sex, not gender, and are predicated on the simplistic assumption that XX = female and XY = male.

Supplemental table S1. Live births, stillbirths and abortions in England and Wales, 1993-2017. Numbers of males and females for live births and stillbirths reflect classifications as recorded on the relevant birth registers. Abortus sex is calculated from the total number of therapeutic and elective abortions on the assumption that the sex ratio ≤ 12 weeks of gestation is 55:45 in favour of females, and 45:55 in favour of males from ≥ 13 weeks of gestation. Total or average values are provided in the bottom rows.

| Year | Live births | | | | Stillbirths | | | | Abortions | | | | Total (live births + stillbirths + abortions) |
|-----------------|-----------------|----------------|----------------|---|--------------|--------------|--------------|--|----------------|----------------|----------------|--|---|
| | Total | Female | Male | Male live births per 1,000 female live births | Total | Female | Male | Male stillbirths per 1000 female stillbirths | Total | Female | Male | Male abortuses per 1000 female abortuses | |
| 1993 | 673467 | 327632 | 345835 | 1056 | 3855 | 1779 | 2076 | 1167 | 157846 | 85072 | 72775 | 855 | 835168 |
| 1994 | 664726 | 323405 | 341321 | 1055 | 3813 | 1779 | 2034 | 1143 | 156539 | 84363 | 72176 | 856 | 825078 |
| 1995 | 648138 | 315950 | 332188 | 1051 | 3600 | 1688 | 1912 | 1133 | 154315 | 83211 | 71104 | 854 | 806053 |
| 1996 | 649485 | 315995 | 333490 | 1055 | 3539 | 1731 | 1808 | 1044 | 167916 | 90444 | 77472 | 857 | 820940 |
| 1997 | 642093 | 313021 | 329072 | 1051 | 3439 | 1638 | 1801 | 1100 | 170145 | 91732 | 78413 | 855 | 815677 |
| 1998 | 635901 | 309998 | 325903 | 1051 | 3417 | 1595 | 1822 | 1142 | 177871 | 95875 | 81996 | 855 | 817189 |
| 1999 | 621872 | 302617 | 319255 | 1055 | 3305 | 1578 | 1727 | 1094 | 173701 | 93634 | 80067 | 855 | 798878 |
| 2000 | 604441 | 294816 | 309625 | 1050 | 3203 | 1472 | 1731 | 1176 | 175542 | 94485 | 81057 | 858 | 783186 |
| 2001 | 594634 | 289999 | 304635 | 1050 | 3159 | 1434 | 1725 | 1203 | 176364 | 94851 | 81513 | 859 | 774157 |
| 2002 | 596122 | 290059 | 306063 | 1055 | 3372 | 1565 | 1807 | 1155 | 175932 | 94542 | 81390 | 861 | 775426 |
| 2003 | 621469 | 303041 | 318428 | 1051 | 3585 | 1711 | 1874 | 1091 | 181582 | 97557 | 84025 | 861 | 806636 |
| 2004 | 639721 | 311381 | 328340 | 1054 | 3686 | 1736 | 1950 | 1123 | 185415 | 99690 | 85725 | 860 | 828822 |
| 2005 | 645835 | 315235 | 330600 | 1049 | 3483 | 1687 | 1796 | 1065 | 186416 | 100535 | 85881 | 854 | 835734 |
| 2006 | 669601 | 327172 | 342429 | 1047 | 3602 | 1741 | 1861 | 1069 | 193737 | 104469 | 89268 | 854 | 866940 |
| 2007 | 690013 | 335525 | 354488 | 1057 | 3598 | 1691 | 1907 | 1128 | 198499 | 107139 | 91360 | 853 | 892110 |
| 2008 | 708711 | 345748 | 362963 | 1050 | 3617 | 1722 | 1895 | 1100 | 195296 | 105514 | 89782 | 851 | 907624 |
| 2009 | 706248 | 344113 | 362135 | 1052 | 3688 | 1730 | 1958 | 1132 | 189100 | 103114 | 85986 | 834 | 899036 |
| 2010 | 723165 | 352199 | 370966 | 1053 | 3714 | 1745 | 1969 | 1128 | 189574 | 102582 | 86992 | 848 | 916453 |
| 2011 | 723913 | 352939 | 370974 | 1051 | 3811 | 1791 | 2020 | 1128 | 189931 | 102787 | 87144 | 848 | 917655 |
| 2012 | 729674 | 355328 | 374346 | 1054 | 3558 | 1674 | 1884 | 1125 | 185122 | 100150 | 84972 | 848 | 918354 |
| 2013 | 698512 | 340129 | 358383 | 1054 | 3284 | 1565 | 1719 | 1098 | 185331 | 100360 | 84971 | 847 | 887127 |
| 2014 | 695233 | 338461 | 356772 | 1054 | 3254 | 1602 | 1652 | 1031 | 184571 | 99998 | 84573 | 846 | 883058 |
| 2015 | 697852 | 339716 | 358136 | 1054 | 3147 | 1498 | 1649 | 1092 | 185824 | 100649 | 85175 | 846 | 886823 |
| 2016 | 696271 | 339225 | 357046 | 1053 | 3112 | 1560 | 1552 | 995 | 185596 | 100501 | 85095 | 847 | 884979 |
| 2017 | 679106 | 331035 | 348071 | 1051 | 2873 | 1347 | 1526 | 1133 | 189859 | 102488 | 87371 | 853 | 871838 |
| Total: | 16656203 | 8114739 | 8541464 | - | 86714 | 41059 | 45655 | - | 4512024 | 2435740 | 2076284 | - | 21254941 |
| Average: | 666248 | 324590 | 341659 | 1053 | 3469 | 1642 | 1826 | 1112 | 180481 | 97430 | 83051 | 853 | 850198 |

Supplemental table S2. Predicted spontaneous abortions (miscarriages) in England and Wales, 1993-2017. The number of conceptions is calculated on the assumption that the sum of live births, stillbirths and elective and therapeutic abortions represents 67% of all conceptions (i.e. 33% of conception are lost). The sex ratio at conception is equal, and so the number of miscarriages can be calculated from the number of males or females conceived and the number accounted for in live birth, stillbirth or abortion statistics. Total or average values are provided in the bottom rows.

| | Number of conceptions | | | Number of conceptions accounted for in live birth stillbirth and abortion data | | | Number of miscarriages | | | |
|-----------------|-----------------------|-----------------|-----------------|--|-----------------|-----------------|------------------------|----------------|----------------|--|
| | Total | Female | Male | Total | Female | Male | Total | Female | Male | Male miscarriages per 1000 female miscarriages |
| 1993 | 1110773 | 555387 | 555387 | 835168 | 414483 | 420686 | 275605 | 140904 | 134701 | 956 |
| 1994 | 1097354 | 548677 | 548677 | 825078 | 409547 | 415531 | 272276 | 139130 | 133146 | 957 |
| 1995 | 1072050 | 536025 | 536025 | 806053 | 400849 | 405204 | 265997 | 135176 | 130822 | 968 |
| 1996 | 1091850 | 545925 | 545925 | 820940 | 408170 | 412770 | 270910 | 137755 | 133155 | 967 |
| 1997 | 1084850 | 542425 | 542425 | 815677 | 406391 | 409286 | 269173 | 136034 | 133139 | 979 |
| 1998 | 1086861 | 543431 | 543431 | 817189 | 407468 | 409721 | 269672 | 135963 | 133709 | 983 |
| 1999 | 1062508 | 531254 | 531254 | 798878 | 397829 | 401049 | 263630 | 133425 | 130205 | 976 |
| 2000 | 1041637 | 520819 | 520819 | 783186 | 390773 | 392413 | 258451 | 130046 | 128405 | 987 |
| 2001 | 1029629 | 514814 | 514814 | 774157 | 386284 | 387873 | 255472 | 128531 | 126941 | 988 |
| 2002 | 1031317 | 515658 | 515658 | 775426 | 386166 | 389260 | 255891 | 129492 | 126399 | 976 |
| 2003 | 1072826 | 536413 | 536413 | 806636 | 402309 | 404327 | 266190 | 134104 | 132086 | 985 |
| 2004 | 1102333 | 551167 | 551167 | 828822 | 412807 | 416015 | 273511 | 138360 | 135151 | 977 |
| 2005 | 1111526 | 555763 | 555763 | 835734 | 417457 | 418277 | 275792 | 138306 | 137486 | 994 |
| 2006 | 1153030 | 576515 | 576515 | 866940 | 433382 | 433558 | 286090 | 143133 | 142957 | 999 |
| 2007 | 1186506 | 593253 | 593253 | 892110 | 444355 | 447755 | 294396 | 148898 | 145498 | 977 |
| 2008 | 1207140 | 603570 | 603570 | 907624 | 452984 | 454640 | 299516 | 150586 | 148930 | 989 |
| 2009 | 1195718 | 597859 | 597859 | 899036 | 448957 | 450079 | 296682 | 148902 | 147780 | 992 |
| 2010 | 1218882 | 609441 | 609441 | 916453 | 456526 | 459927 | 302429 | 152915 | 149514 | 978 |
| 2011 | 1220481 | 610241 | 610241 | 917655 | 457517 | 460138 | 302826 | 152724 | 150102 | 983 |
| 2012 | 1221411 | 610705 | 610705 | 918354 | 457152 | 461202 | 303057 | 153554 | 149503 | 974 |
| 2013 | 1179879 | 589939 | 589939 | 887127 | 442054 | 445073 | 292752 | 147885 | 144867 | 980 |
| 2014 | 1174467 | 587234 | 587234 | 883058 | 440061 | 442997 | 291409 | 147172 | 144237 | 980 |
| 2015 | 1179475 | 589737 | 589737 | 886823 | 441863 | 444960 | 292652 | 147874 | 144777 | 979 |
| 2016 | 1177022 | 588511 | 588511 | 884979 | 441286 | 443693 | 292043 | 147225 | 144818 | 984 |
| 2017 | 1159545 | 579772 | 579772 | 871838 | 434870 | 436968 | 287707 | 144903 | 142804 | 986 |
| Total: | 28269072 | 14134536 | 14134536 | 21254941 | 10591538 | 10663403 | 7014131 | 3542998 | 3471133 | - |
| Average: | 1130763 | 565381 | 565381 | 850198 | 423662 | 426536 | 280565 | 141720 | 138845 | 980 |