Supporting Information

Orzack et al. 10.1073/pnas.1416546112

SI Text

FISH Probes Used to Karyotype ART Embryos. The FISH probes and their target locus and region (both in parentheses) were X chromosome: CEP X (DXZ1, p11.1-q11.1), Y chromosome: CEP Y Alpha Satellite at Genzyme Genetics (DYZ3, p11.1-q11.1), and CEP Y Satellite III at Reprogenetics (DYZ1, q12), chromosome 8: CEP 8 (D8Z2, p11.1-q11.1), chromosome 9: CEP 9 Alpha Satellite at Genzyme Genetics (unknown, p11.1-q11), chromosome 13: LSI 13 (RB1, q14.1-q14.3), chromosome 14 at Reprogenetics: TelVysion 14q (STS-X58399/SHGC-36156/STS/AA034492/telomeric IGHV segments, q32.3), chromosome 15: CEP 15 Alpha Satellite (D15Z4, p11.1-q11.1), chromosome 16: CEP 16 Satellite II (D16Z3, q11.2), chromosome 17: CEP 17 at Reprogenetics (D17Z1, p11.1- q11.1), chromosome 18: CEP 18 (D18Z1, p11.1-q11), chromosome 20 at Reprogenetics: TelVysion 20p (D20S1157, p13), chromosome 21: LSI 21 (D21S259/D21S341/D21S342, q22.13-q22.2), and chromosome 22: LSI 22q (BCR, q11.2). Details of sample preparation and protocols are available on request (see refs. 1 and 2 for protocols used at Reprogenetics). All probes were obtained from Abbott Molecular (www.abbottmolecular.com).

Summary of Induced Abortion Studies. The 41 studies of the sex ratio of induced abortions are shown in Table S1.

Procedures Used to Process CVS and Amniocentesis Samples. Cells were cultured following refs. 3–5. Cell suspensions were placed on coverslips in Petri dishes containing growth media. After 5–10 d, a mitotic inhibitor (colcemid) was added. Cells were harvested by removing the media and mitotic inhibitor and adding a hypotonic solution, followed by changes of fixative (3:1 methanol to acetic acid). The cells were dried, thereby breaking the nuclei of dividing cells and spreading the chromosomes. After treatment with trypsin, chromosomal bands were visualized with Wright-Giemsa stain. Images of at least four metaphase cells per sample were recorded, and karyotypes were recorded for two or three cells.

Week-Specific Estimates of the CSR Based on Fetal-Death and Live-Birth Data for the US 1995–2004. Data for weeks postconception (CA) based on LMP are shown in Table S2.

Mixed-Effect Analyses of the Association Between the State of Individual Chromosomes in ART Embryos and the Cohort Sex Ratio. Analyses of the combined FISH and aCGH data are shown in Table S3.

Mixed-Effect Analyses of the Association Between the Overall State of the Embryo (Any) or the State of Individual Chromosomes and the Cohort Sex Ratio. Analyses of the aCGH data for blastomere samples and blastocyst samples are shown in Table S4.

Mixed-Effect Analyses of the Association Between the Overall State of the Embryo (Any) or the State of Individual Chromosomes and the Cohort Sex Ratio. Analyses of blastomere samples (FISH only) and blastocyst samples (aCGH) are shown in Table S5.

Nine Reasons Why ART Embryos Provide a Meaningful CSR Estimate. ***The birth sex ratio of babies conceived via ART matches the birth sex ratio of babies conceived naturally.*** The birth sex ratio arising from our sample of ART embryos is unknown. We analyzed data from the Australian Institute of Health and Welfare (www.npesu.unsw.edu.au/surveillance-reports); this is the largest comparison of ART and natural sex ratios to date. As shown in Table S6, the sex ratio of ART births (0.515, 95% CI: 0.512–0.517, n = 136,647) and the sex ratio of natural births (0.514, 95% CI: 0.514–0.514, n = 5,500,467) are statistically identical. These estimates match previous results. Ref. 6 (table 3) reported an ART birth sex ratio for Denmark from 1995 to 2000 of 0.521 (95% CI: 0.511–0.531, n = 8,894) and a sex ratio for all births from 1995 to 2004 of 0.513 (95% CI: 0.512–0.515, n = 663,276). Other smaller studies reporting this overlap include refs. 7–10. However, ref. 11 (p. 1582) reported an ART sex ratio of 0.498 (95% CI: 0.490–0.506, n = 15,164) and a sex ratio for 2005 US births of 0.512 (95% CI: 0.511–0.512, n = 4,138,349).

Our overall conclusion is that ART generates a cohort of fetuses whose fates during pregnancy match those of naturally conceived fetuses.

The birth sex ratio for ART with in vivo conception and the birth sex ratio for ART with in vitro conception appear to be identical. We assessed the influence of in vivo vs. in vitro conception by comparing standard ART and gametic intrafallopian transfer (GIFT) birth sex ratios. This comparison holds constant the influence of in vitro treatment of eggs and sperm; standard ART involves a variety of artificial conception methods and GIFT involves natural conception. We analyzed data collected by the Australian Institute of Health and Welfare. As shown in Table S7, the sex ratio for GIFT is 0.521 (95% CI: 0.511–0.531, n = 9,312) compared with the estimate for ART (0.515, 95% CI: 0.512–0.517; Table S6); almost all of the ART births involved IVF and ICSI and not GIFT. We conclude that there is no influence of in vitro conception per se on the birth sex ratio.

Our estimate of the PSR matches the value expected given unbiased segregation of sex chromosomes during spermatogenesis and unbiased fertilization. We further note that this match occurs despite geographic and temporal heterogeneity of samples (embryos came from ART clinics across the United States and other countries between 1995 and 2009). There is no evidence that spermatogenesis results in a ratio of X- and Y-bearing sperm similar to the sex ratio bias among births. Instead, studies suggest that spermatogenesis results in an unbiased ratio of X- and Y-bearing sperm (12–15) or perhaps a slight bias (toward X chromosome-bearing sperm) (16–18). In addition, segregation of other human chromosomes appears to be unbiased.

Analyses of data from other species do not provide conclusive evidence that the mammalian PSR is male-biased. There are nonmolecular estimates (derived from sex chromatin or karyotyping) and molecular estimates. The nonmolecular estimates should be interpreted cautiously for four reasons. First, scoring sex chromatin likely overestimates the number of males (19). Second, some estimates are based on fetal morphology, which can be unreliable, especially for early fetuses. Third, some estimates are based on an amalgamation of embryos and fetuses. Fourth, some studies based their estimate only on the sex ratio at birth. The molecular estimates involve protein-based and DNA-based techniques (20, 21). Estimates are shown in Table S8.

We analyzed these data (without phylogenetic correction) with a mixed-effect analysis in which studies within species were treated as random effects and species were treated as factors. We analyzed the nonmolecular data and the molecular data separately; in both cases, there is substantially more support for the model with an overall sex ratio compared with the species-specific model. The overall nonmolecular estimate is 0.531 (95% CI: 0.516–0.547), and the overall molecular estimate is 0.498 (95% CI: 0.485–0.512). The latter, more reliable, estimate does not provide compelling evidence that the PSR is male-biased in mammals.

We note that there is also no indication that the sex ratio at birth in mammals is usually male-biased (22, p. 400).

The method of in vitro conception does not appear to influence the ART estimate of the CSR. The method of conception is known for a subset of embryos in our FISH sample (n = 8,214). These embryos were conceived via standard ART (IVF) or via intracytoplasmic sperm injection (ICSI). We assigned random effects to women and treated method of conception as a factor (this sample contained only a single procedure for each woman). Support for the two models is comparable; the overall CSR is 0.508 (95% CI: 0.496–0.519, n = 8,214); this is similar to the estimate for the entire sample (0.502) in Table 1. The IVF estimate is 0.518 (95% CI: 0.502–0.533, n = 4,361), and the ICSI estimate is 0.496 (95% CI: 0.480–0.513, n = 3,853). Neither conception method is the same as natural conception, but we caution against simple conclusions as to which one is more like natural conception, especially given the lack of evidence for a difference in the associated sex ratios.

A high proportion of early naturally conceived embryos may be abnormal (as in our ART sample). A high proportion of abnormal ART embryos has been previously reported (23, 24). Very few naturally conceived embryos less than 1 wk old have been studied, but some authors reported abnormalities (25–38); to our knowledge, none of these embryos has been karyotyped.

There are three kinds of circumstantial evidence that many naturally conceived embryos are karyotypically abnormal. First, possibly up to 70–80% of conceptions fail (even among young mothers). Perhaps 50% fail subclinically within the first few weeks (39–61). Much mortality may be caused by an abnormal karyotype (57, 62); many spontaneous abortuses have karyotypic abnormalities (63–73). Second, oogenesis is error prone (74–77). Spermatogenesis appears to be less error prone; a few percent of sperm are abnormal (15). Karyotypically abnormal gametes can form zygotes (78–82). Third, mitotic errors occur frequently in cleavage-stage embryos and in blastocysts (56, 83, 84). Limited evidence suggests that the frequencies of karyotypic abnormalities in embryos conceived in vitro and in vivo differ in some species (85, 86) but not all (87).

Typical methods for collection and preparation of gametes (88, 89) appear to have little or no influence on the birth sex ratio. For example, it is likely that many embryos in our sample were derived from oocytes collected after ovarian stimulation via gonadotropin or clomiphene citrate (90). Limited data indicate that the birth sex ratio after such stimulation (but with natural conception) does not differ from the sex ratio without stimulation (91). The typical techniques used to capacitate sperm have little influence on the sex ratio of ART births (92). In addition, limited data indicate that embryos derived from unstimulated oocytes and those derived from stimulated oocytes have similar frequencies of abnormality (93).

The average age difference between women who use ART and women who conceive naturally does not imply that ART embryos are unsuitable as a basis for an estimate of the PSR. Women who use ART are not a random sample of pregnant women. For example, the average mother's age in our sample is 36.6 y, which is older than the average mother's age in the United States. However, young women who use ART, but not for fertility problems, produce a high percentage of karyotypically abnormal embryos (94, 95), which suggests that age and fertility problems do not cause this high percentage (96, 97). It is believed that most such embryos arise from abnormal oocytes and that the rate of meiotic aneuploidy in oocytes increases with age (98). However, such an increase has not always been observed (99). In addition, aneuploidy increases linearly with age for some chromosomes (100, 101), whereas for others, it increases only after age 40 y (102).

Ionic strength, pH, and temperature during fertilization and early development vary across ART protocols but are not grossly different from in vivo conditions as far as they are known (103–105). Much progress has been made at characterizing in vivo conditions (106–110). We know of no evidence that known differences between in vitro and in vivo conditions affect the in vivo sex ratio (111) or that in vitro conditions affect the birth sex ratio. However, we acknowledge that even small differences between in vitro and in vivo conditions might cause a difference in their associated sex ratios.

The Implications of Our Results for Understanding of the Evolution of the Human Sex Ratio. Extending the argument of Düsing (112), Fisher (113) claimed that the evolutionary equilibrium resulting from the long-term process of natural selection on the sex ratio was equal investment in the two sexes at "the end of the period of parental expenditure." The evolution of this equilibrium is driven by a Darwinian dynamic in which individuals or couples whose heritable investment in the two sexes is closer to equal gain higher representation in the population over the long-term. All other things being equal, this process of selection among individuals or couples stops when the evolutionary equilibrium of equal investment is attained, i.e., the population as a whole invests equal amounts into the two sexes of offspring (114, 115). Specific assumptions are needed in order to generate the prediction that an individual or a couple produce equal investment when the population is at the equal investment equilibrium (116).

Fisher claimed that the human sex ratio has evolved to an equal investment equilibrium at the end of parental expenditure via the Darwinian process described above. He did not state at what age of offspring the end occurs. However, he did describe the trajectory of the sex ratio of a cohort from conception to the equal investment equilibrium. He stated that more males are conceived than females and implied that the equilibrium is approached monotonically due to higher mortality of males between conception and the end of parental expenditure (p. 159). Fisher did not specifically predict that the sex ratio is 0.5 when parental expenditure ends (this prediction depends on assumptions about energy investment and mortality schedules that may not be true for humans); nonetheless, many scientists believe that this sex ratio is the outcome predicted by Fisher. Our results suggest that the CSR starts at 0.5, becomes female-biased, reattains 0.5, becomes male-biased, and decreases past 0.5. Whatever equilibrium one might specify, this trajectory indicates that the CSR does not exhibit a monotonic trajectory like the one implied by Fisher.

We can still heuristically assess whether the equal investment equilibrium is attained in a human population. We stress that data on the sex specificity and timing of investment are required if any claims are to go beyond crude speculation. Equal investment is predicted for age-structured populations (117), given random mating of individuals of different ages and little or no influence of parental age on the sex ratio produced. We assume that the net energetic cost of a son and of a daughter are equal at the end of parental investment; this implies that the sex ratio will be 0.5 at that age. We also assume that data from a single cohort are sufficient to test this prediction.

Age-specific estimates of the sex ratio can be obtained using the estimated numbers of males and females resident in the US who were born in 1900 (Table S9); their sex ratio trajectory is essentially complete. (Data for ages 0–79 y are available at www.census.gov/popest/data/national/asrh/pre-1980/PE-11.html. Data for ages 80–89 y are available at www.census.gov/popest/data/national/asrh/1980s/80s_nat_detail.html, and data for ages 90–99 y are available at www.census.gov/popest/data/intercensal/national/index.html. Data for ages 100+ y for this cohort are not available. Census estimates of the sex ratio of this cohort are available only for ages 0, 10, 20, and 30 y.) These sex ratio estimates are not CSRs because they are defined by age from birth, not by age from conception.

The sex ratio at age 18 y was 0.488 (95% CI: 0.487–0.489, n = 1,843,000). At age 40 y, it was 0.501 (95% CI: 0.500–0.501, n = 1,823,210). At age 60, it was 0.483 (95% CI: 0.482–0.484, n = 1,525,828). If parental expenditure ends at age 40 y, these data support the prediction of 0.5. This adaptationist conclusion would be more credible if we understood why natural selection has not eliminated the high level of prebirth mortality, especially when it appears to result in no net change in the sex ratio from conception to age 40 y. The failure of three-quarters of conceptions to reach sexual maturity engenders energetic costs, which presumably could be eliminated to the evolutionary benefit of parents. Alternatively, such "screening" could be beneficial to parents. We take no position and stress the need to consider the totality of evidence when making adaptive claims about the human sex ratio and human pregnancy (118–121). We emphasize that our analysis of the 1900 cohort data illustrates how little one conclude about the adaptive significance of the human sex ratio without data on investment, even when the analysis is based on age-specific sex ratio estimates that are among the best available. This ambiguity is an important cautionary lesson, which is underscored by our result that female mortality during pregnancy may be greater than male mortality. All other things being equal, this greater female mortality implies that the sex ratio at investment equilibrium should be male-biased.

The 1900 cohort data can also be compared with the predictions of Charlesworth's (122) model of sex ratio evolution for an age-structured population. His evolutionarily stable strategy model predicts that the PSR is male-biased and that the age-specific sex ratio attains a female-biased equilibrium value (p. 356) by "the end of the first year of postnatal life"; Charlesworth defined parental investment solely as the production of offspring plus the replacement of offspring lost during pregnancy or soon thereafter. As such, his model is at best applied to our primate ancestors or to those human groups and societies in which the human sex ratio might have evolved. Nonetheless, he asserted that his "firm prediction" of a female bias at the "end of infancy" is confirmed in "pre-industrial" societies, although he did not provide sex ratio data. The 1900 cohort exhibits significantly male-biased sex ratios until age 15, which are not consistent with his prediction. This cohort presumably does not qualify as "pre-industrial"; however, sex ratios in hunter–gatherer, horticultural, and pastoral societies are most often similarly male-biased at birth and at age 15 y (123).

Finally, we note that it is not self-evident that the sex ratio trajectory of a human cohort attains any fixed value (apart from sampling error) before only one sex remains. For example, the sex ratio for the 1900 cohort declines throughout life (although not monotonically). Sex ratio estimates are male-biased until age 15 y, after which almost all are between 0.48 and 0.5 until age 61 y. Estimates then become increasingly female-biased and will attain a value of 0.0, because the oldest humans are female (124). Static idealization of a trait can be misleading if dynamic expression is a central component of a trait's evolutionary response to natural selection (125–127). For the 1900 cohort, perhaps the midlife sex ratios ranging from 0.48 to 0.5 can be idealized as a trait that is a target of natural selection. Determining the validity of this static idealization that the ultimate target of natural selection is a single sex ratio (as opposed to the target being, say, an age-specific sequence of sex ratios) will require data on the sex specificity and timing of parental investment, statistical assessment of the age-specific sex ratios to determine whether they are reasonably regarded as age invariant, and a comparison of the predictive accuracy of relevant static and dynamic adaptive models.

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Table S1. Summary of induced abortion studies

Study	Sex ratio	Males	Females	Sexing method
Bochkov and Kostrova (1)	0.489	440	460	C
Bochkov and Kostrova (2)*	0.508	1,525	1,475	C
Boué et al. (3)	0.600	21	14	K
Bowen and Lee (4)	0.714	5	2	K
Bunak (5)	0.611	33	21	M
Csordas et al. (6)	0.560	560	440	C
Evdokimova et al. (7)	0.526	41	37	K
Goldstein et al. (8)	0.376	35	58	C
Golovachev et al. (9)	0.327	16	33	K
Hahnemann (10)	0.500	86	86	K
Hnevkovsky et al. (11)	0.579	378	275	C
Hoshi et al. (12)[†]	0.455	407	487	K
Jakobovits et al. (13)	0.522	391	358	M
Kajii et al. (14)[‡]	0.486	530	561	K
Kellokumpu-Lehtinen and Pelliniemi (15)	0.539	297	254	C
Kerr and Rashad (16)	0.533	8	7	K
Klinger and Glasser (17)[§]	0.506	746	727	K
Kukharenko (18)	0.587	595	419	C
Kukharenko (19)	0.497	349	353	C
Lee and Takano (20)	0.605	848	554	H
Matsunaga et al. (21)	0.514	95	90	C
Matthiessen and Matthiessen (22)	0.580	459	332	M
Mikamo (23)[¶]	0.518	381	355	C
Momoli and Volet (24)	0.543	69	58	C
Moore and Hyrniuk (25)	0.475	131	145	C
Ohama (26)	0.505	545	534	K
Pogolrzelska (27)	0.531	69	61	C
Sasaki (28)[‖]	0.469	452	511	K
Schultze (29)	0.700	156	67	C
Serr and Ismajovich (30)	0.624	78	47	C
Stonova and Selezniova (31)	0.615	8	5	K
Suzomori (32)	0.600	6	4	K
Szontagh (33)**	0.550	165	135	C
Szulman (34)	0.733	11	4	K
Thiede and Metcalfe (35)[††]	0.595	22	15	C, K
Tonomura et al. (36)[‡‡]	0.534	325	284	K
Tsuji and Nakano (37)	0.477	122	134	K
Vaida (38)	0.579	123	91	C
Yamamoto (39)[§§]	0.518	570	530	K
Yasuda et al. (40)	0.439	65	83	K
Zhou et al. (41)	0.537	630	542	K

All but two studies assigned fetuses to trimester. Twenty-four studies assigned gestational age in weeks or a narrow range of weeks. In almost all cases, age was based on an estimate of the LMP. C, chromatin; H, histology; K, karyotype; M, morphology.

*Included results from Kostrova (42).

†Probably included results from Hoshi et al. (43).

‡Probably included results from Kajii et al. (44).

§Included results from Klinger et al. (45).

¶Identical to Mikamo (46).

‖Included results from Makino and Sasaki (47), Makino et al. (48, 49), Sasaki et al. (50, 51), Shimba (52), Makino (53), and Makino et al. (54).

**Identical to Szontagh et al. (55).

††Included results from Thiede and Salm (56).

‡‡Included results from Tonomura et al. (57).

§Included results from Yamamoto et al. (58–60).

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Table S2. Week-specific estimates of the CSR based on fetal-death and live-birth data for the United States from 1995 to 2004

Week	Sex ratio	Males	Females
18	0.512	18,162,805	17,335,131
19	0.512	18,149,803	17,325,305
20	0.512	18,133,380	17,311,832
21	0.512	18,115,431	17,296,645
22	0.512	18,096,738	17,280,309
23	0.512	18,075,460	17,261,458
24	0.511	18,052,256	17,240,668
25	0.511	18,026,483	17,217,305
26	0.511	17,997,574	17,191,404
27	0.511	17,958,594	17,157,699
28	0.511	17,912,050	17,117,048
29	0.511	17,850,789	17,062,918
30	0.511	17,769,904	16,991,973
31	0.511	17,655,443	16,892,387
32	0.511	17,484,850	16,745,317
33	0.510	17,200,884	16,498,846
34	0.510	16,736,525	16,095,007
35	0.508	15,925,796	15,394,480
36	0.506	14,362,094	14,035,032
37	0.501	11,273,505	11,245,724
38	0.495	6,934,085	7,076,644
39	0.493	3,238,602	3,334,960
40	0.493	1,298,124	1,337,331
41	0.493	646,232	663,458
42	0.493	330,479	339,250
43	0.493	163,099	167,812
44	0.495	75,062	76,481
45	0.499	28,537	28,674

Week is defined postconception (CA) as determined by LMP.

Table S3. Mixed-effect analyses of the association between the state of individual chromosomes in ART embryos and the CSR

Chromosome	Embryos	CSR	*N*	ΔAIC	Akaike weight
XY	All	0.505	20,116	341.468	<0.001
	Abnormal	0.999	323	0	>0.999
	Normal	0.498	19,793		
1	All	0.499	20,263	0	0.988
	Abnormal	0.524	452	8.776	0.012
	Normal	0.498	19,811		
2	All	0.498	20,278	0	0.992
	Abnormal	0.510	467	9.750	0.008
	Normal	0.498	19,811		
3	All	0.498	20,068	0	0.992
	Abnormal	0.485	257	9.499	0.008
	Normal	0.498	19,811		
4	All	0.498	20,200	0	0.985
	Abnormal	0.523	389	8.358	0.015
	Normal	0.498	19,811		
5	All	0.498	20,117	0	0.988
	Abnormal	0.524	306	8.823	0.012
	Normal	0.498	19,811		
6	All	0.498	20,108	0	0.992
	Abnormal	0.512	297	9.757	0.008
	Normal	0.498	19,811		
7	All	0.497	20,155	0	0.967
	Abnormal	0.462	344	6.756	0.033
	Normal	0.498	19,811		
8	All	0.498	20,223	0	0.991
	Abnormal	0.480	412	9.404	0.009
	Normal	0.498	19,811		
9	All	0.498	20,229	0	0.991
	Abnormal	0.486	418	9.430	0.009
	Normal	0.498	19,811		
10	All	0.498	20,166	0	0.991
	Abnormal	0.516	355	9.416	0.009
	Normal	0.498	19,811		
11	All	0.498	20,133	0	0.991
	Abnormal	0.478	322	9.445	0.009
	Normal	0.498	19,811		
12	All	0.498	20,026	0	0.992
	Abnormal	0.486	215	9.607	0.008
	Normal	0.498	19,811		
13	All	0.498	20,286	0	0.993
	Abnormal	0.503	475	9.876	0.007
	Normal	0.498	19,811		
14	All	0.499	20,285	0	0.981
	Abnormal	0.522	474	7.868	0.019
	Normal	0.498	19,811		
15	All	0.497	20,607	0	0.961
	Abnormal	0.466	796	6.426	0.039
	Normal	0.498	19,811		
16	All	0.498	21,224	0	0.992
	Abnormal	0.498	1,413	9.764	0.008
	Normal	0.498	19,811		
17	All	0.498	20,103	0	0.990
	Abnormal	0.515	292	9.207	0.010
	Normal	0.498	19,811		
18	All	0.497	20,239	0	0.972
	Abnormal	0.457	448	7.112	0.028
	Normal	0.498	19,811		
19	All	0.499	20,804	0	0.990
	Abnormal	0.509	993	9.183	0.010
	Normal	0.498	19,811		
20	All	0.498	20,190	0	0.977
	Abnormal	0.476	379	7.503	0.023
	Normal	0.498	19,811		

Table S3. Cont.

Chromosome	Embryos	CSR	*N*	ΔAIC	Akaike weight
21	All	0.499	20,673	0	0.985
	Abnormal	0.516	862	8.373	0.015
	Normal	0.498	19,811		
22	All	0.498	21,096	0	0.990
	Abnormal	0.493	1,285	9.167	0.010
	Normal	0.498	19,811		

All scored chromosomes were normal except the target chromosome, which could be normal or abnormal.

Table S4. Mixed-effect analyses of the association between the overall state of the embryo (Any) or the state of individual chromosomes and the CSR (aCGH data)

		Blastomere				Blastocyst			
Chromosome	Embryos	CSR	*N*	ΔAIC	Akaike weight	CSR	*N*	ΔAIC	Akaike weight
Any	All	0.484	12,693	0	0.985	0.507	32476	0	0.898
	Abnormal	0.487	9,384	8.367	0.015	0.511	15,974	4.356	0.102
	Normal	0.474	3,310			0.502	16,502		
XY	All	0.484	12,693	504.835	<0.001	0.507	32,476	570.744	<0.001
	Abnormal	0.812	1,103	0	>0.999	0.999	771	0	>0.999
	Normal	0.453	11,590			0.498	31,705		
1	All	0.484	12,693	0	0.983	0.507	32,476	0	0.991
	Abnormal	0.470	1,768	8.103	0.017	0.498	1,204	9.451	0.009
	Normal	0.486	10,925			0.507	31,272		
2	All	0.484	12,693	0	0.982	0.507	32,476	0	0.929
	Abnormal	0.476	1,598	8.013	0.018	0.479	1,258	5.146	0.071
	Normal	0.485	11,095			0.508	31,218		
3	All	0.484	12,693	0	0.990	0.507	32,476	0	0.982
	Abnormal	0.488	1,355	9.247	0.010	0.483	900	7.990	0.018
	Normal	0.483	11,338			0.507	31,576		
4	All	0.484	12,693	0	0.989	0.507	32,476	0	0.985
	Abnormal	0.474	1,376	8.949	0.011	0.496	1,083	8.347	0.015
	Normal	0.485	11,317			0.507	31,393		
5	All	0.484	12,693	0.652	0.419	0.507	32,476	0	0.992
	Abnormal	0.444	1,481	0	0.581	0.498	1,066	9.656	0.008
	Normal	0.489	11,212			0.507	31,410		
6	All	0.484	12,693	0	0.993	0.507	32,476	0	0.966
	Abnormal	0.480	1,382	9.871	0.007	0.485	983	6.714	0.034
	Normal	0.484	11,311			0.507	31,493		
7	All	0.484	12,693	0	0.943	0.507	32,476	0	0.806
	Abnormal	0.459	1,435	5.626	0.057	0.473	1,202	2.849	0.194
	Normal	0.487	11,258			0.508	31,274		
8	All	0.484	12,693	0	0.991	0.507	32,476	0	0.981
	Abnormal	0.489	1,489	9.357	0.009	0.485	1,149	7.859	0.019
	Normal	0.483	11,204			0.507	31,327		
9	All	0.484	12,693	0	0.993	0.507	32,476	0	0.526
	Abnormal	0.485	1,666	9.885	0.007	0.468	1,344	0.210	0.474
	Normal	0.484	11,027			0.508	31,132		
10	All	0.484	12,693	0	0.985	0.507	32,476	0	0.888
	Abnormal	0.484	1,493	8.402	0.015	0.475	1,190	4.131	0.012
	Normal	0.484	11,200			0.508	31,286		
11	All	0.484	12,693	0	0.993	0.507	32,476	0	0.959
	Abnormal	0.483	1,563	9.983	0.007	0.485	1,185	6.281	0.041
	Normal	0.484	11,130			0.507	31,291		
12	All	0.484	12,693	0	0.992	0.507	32,476	0	0.981
	Abnormal	0.484	1,470	9.653	0.008	0.489	890	7.837	0.019
	Normal	0.484	11,223			0.507	31,586		
13	All	0.484	12,693	0	0.992	0.507	32,476	0	0.963
	Abnormal	0.479	1,683	9.681	0.008	0.486	1,450	6.537	0.037
	Normal	0.485	11,010			0.508	31,026		
14	All	0.484	12,693	0	0.988	0.507	32,476	0	0.986
	Abnormal	0.477	1,729	8.788	0.012	0.494	1,349	8.495	0.014
	Normal	0.485	10,964			0.507	31,127		
15	All	0.484	12,693	0	0.986	0.507	32,476	0	0.990
	Abnormal	0.479	2,047	8.537	0.014	0.500	2,162	9.126	0.010
	Normal	0.485	10,646			0.507	30,314		
16	All	0.484	12,692	0	0.990	0.507	32,476	0	0.969
	Abnormal	0.477	2,428	9.206	0.010	0.513	2,759	6.872	0.031
	Normal	0.485	10,265			0.506	29,717		
17	All	0.484	12,693	0	0.990	0.507	32,476	0	0.979
	Abnormal	0.474	1,674	9.092	0.010	0.488	1,081	7.643	0.021
	Normal	0.485	11,019			0.507	31,395		
18	All	0.484	12,693	0	0.987	0.507	32,476	0	0.755
	Abnormal	0.487	1,682	8.627	0.013	0.473	1,486	2.252	0.245
	Normal	0.483	11,011			0.508	30,990		

Table S4. Cont.

		Blastomere				Blastocyst			
Chromosome	Embryos	CSR	*N*	ΔAIC	Akaike weight	CSR	*N*	ΔAIC	Akaike weight
19	All	0.484	12,693	0	0.993	0.507	32,476	0	0.993
	Abnormal	0.483	2,620	9.966	0.007	0.503	1,879	9.844	0.007
	Normal	0.484	10,073			0.507	30,597		
20	All	0.484	12,693	0	0.993	0.507	32,476	0	0.949
	Abnormal	0.487	1,787	9.854	0.007	0.484	1,426	5.846	0.051
	Normal	0.483	10,906			0.508	31,050		
21	All	0.484	12,693	0	0.993	0.507	32,476	0	0.983
	Abnormal	0.483	2,026	9.873	0.007	0.506	2,336	8.076	0.017
	Normal	0.484	10,667			0.507	30,140		
22	All	0.484	12,693	0	0.952	0.507	32,476	0	0.872
	Abnormal	0.469	2,184	5.976	0.048	0.488	2,914	3.837	0.128
	Normal	0.487	10,509			0.509	29,562		

Table S5. Mixed-effect analyses of the association between the overall state of the embryo (Any) or the state of individual chromosomes and the CSR) for blastomeres (FISH only) and blastocysts (aCGH)

		Blastomere				Blastocyst			
Chromosome	Embryos	CSR	*N*	ΔAIC	Akaike weight	CSR	*N*	ΔAIC	Akaike weight
Any	All	0.503	94,535	31.275	<0.001	0.507	32,476	0	0.898
	Abnormal	0.511	59,524	0	>0.999	0.511	15,974	4.356	0.102
	Normal	0.490	35,011			0.502	16,502		
XY	All	0.503	94,535	533.156	<0.001	0.507	32,476	570.744	<0.001
	Abnormal	0.589	16,282	0	>0.999	0.999	771	0	>0.999
	Normal	0.486	78,253			0.498	31,705		
1	All	—	—	—	—	0.507	32,476	0	0.991
	Abnormal	—	—	—	—	0.498	1,204	9.451	0.009
	Normal	—	—	—	—	0.507	31,272		
2	All	—	—	—	—	0.507	32,476	0	0.929
	Abnormal	—	—	—	—	0.479	1,258	5.146	0.071
	Normal	—	—	—	—	0.508	31,218		
3	All	—	—	—	—	0.507	32,476	0	0.982
	Abnormal	—	—	—	—	0.483	900	7.990	0.018
	Normal	—	—	—	—	0.507	31,576		
4	All	—	—	—	—	0.507	32,476	0	0.985
	Abnormal	—	—	—	—	0.496	1,083	8.347	0.015
	Normal	—	—	—	—	0.507	31,393		
	All	—	—	—	—	0.507	32,476	0	0.992
	Abnormal	—	—	—	—	0.498	1,066	9.656	0.008
	Normal	—	—	—	—	0.507	31,410		
6	All	—	—	—	—	0.507	32476	0	0.966
	Abnormal	—	—	—	—	0.485	983	6.714	0.034
	Normal	—	—	—	—	0.507	31,493		
7	All	—	—	—	—	0.507	32,476	0	0.806
	Abnormal	—	—	—	—	0.473	1,202	2.849	0.194
	Normal	—	—	—	—	0.508	31,274		
8	All	0.505	22,113	0	0.984	0.507	32,476	0	0.981
	Abnormal	0.503	4,119	8.274	0.016	0.485	1,149	7.859	0.019
	Normal	0.506	17,994			0.507	31,327		
9	All	0.524	3,678	0	0.947	0.507	32,476	0	0.526
	Abnormal	0.516	655	5.780	0.053	0.468	1,344	0.210	0.474
	Normal	0.526	3,023			0.508	31,132		
10	All	—	—	—	—	0.507	32,476	0	0.888
	Abnormal	—	—	—	—	0.475	1,190	4.131	0.012
	Normal	—	—	—	—	0.508	31,286		
11	All	—	—	—	—	0.507	32,476	0	0.959
	Abnormal	—	—	—	—	0.485	1,185	6.281	0.041
	Normal	—	—	—	—	0.507	31,291		
12	All	—	—	—	—	0.507	32,476	0	0.981
	Abnormal	—	—	—	—	0.489	890	7.837	0.019
	Normal	—	—	—	—	0.507	31,586		
13	All	0.503	89,263	0	0.976	0.507	32,476	0	0.963
	Abnormal	0.505	23,598	12.075	0.024	0.486	1,450	6.537	0.037
	Normal	0.503	65,665			0.508	31,026		
14	All	0.503	18,378	0	0.992	0.507	32,476	0	0.986
	Abnormal	0.500	4,727	9.542	0.008	0.494	1,349	8.495	0.014
	Normal	0.504	13,651			0.507	31,127		
15	All	0.500	78,437	42.555	<0.001	0.507	32,476	0	0.990
	Abnormal	0.518	24,120	0	>0.999	0.500	2,162	9.126	0.010
	Normal	0.492	54,317			0.507	30,314		
16	All	0.504	79,589	0	0.881	0.507	32,476	0	0.969
	Abnormal	0.508	24,097	7.213	0.119	0.513	2,759	6.872	0.031
	Normal	0.502	55,492			0.506	29,717		
17	All	0.502	76,327	9.821	0.007	0.507	32,476	0	0.979
	Abnormal	0.517	18,489	0	0.993	0.488	1,081	7.643	0.021
	Normal	0.498	57,838			0.507	31,395		
18	All	0.503	88,607	0	0.796	0.507	32,476	0	0.755
	Abnormal	0.510	23,587	2.717	0.204	0.473	1,486	2.252	0.245
	Normal	0.500	65,020			0.508	30,990		

Table S5. Cont.

		Blastomere				Blastocyst			
Chromosome	Embryos	CSR	*N*	ΔAIC	Akaike weight	CSR	*N*	ΔAIC	Akaike weight
19	All	—	—	—	—	0.507	32,476	0	0.993
	Abnormal	—	—	—	—	0.503	1,879	9.844	0.007
	Normal	—	—	—	—	0.507	30,597		
20	All	0.502	17,866	0	0.969	0.507	32,476	0	0.949
	Abnormal	0.497	4,896	6.910	0.031	0.484	1,426	5.846	0.051
	Normal	0.504	12,970			0.508	31,050		
21	All	0.503	89,669	0	0.973	0.507	32,476	0	0.983
	Abnormal	0.510	25,434	7.151	0.027	0.506	2,336	8.076	0.017
	Normal	0.500	64,235			0.507	30,140		
22	All	0.504	80,548	0	0.992	0.507	32,476	0	0.872
	Abnormal	0.503	25,218	9.567	0.008	0.488	2,914	3.837	0.128
	Normal	0.504	55,330			0.509	29,562		

Table S6. Birth sex ratios for ART conceptions and for natural conceptions in Australia and New Zealand between 1979 and 2011

	ART			Natural		
Year	Sex ratio	Males	Females	Sex ratio	Males	Females
1991	0.516*	3,554	3,329	0.516	128,738	120,972
1992	0.528	702	628	0.514	134,317	126,961
1993	0.529	807	719	0.515	133,289	125,480
1994	0.515	1,029	968	0.515	133,525	125,583
1995	0.498	1,216	1,226	0.514	132,492	125,031
1996	0.514	1,416	1,340	0.515	130,967	123,279
1997	0.523	1,993	1,815	0.514	129,614	122,708
1998	0.521	2,174	1,999	0.513	128,928	122,340
1999	0.516	2,443	2,287	0.513	129,714	122,913
2000	0.512	2,699	2,571	0.514	129,407	122,502
2001				0.514	130,647	123,581
2002	0.511	3,543	3,386	0.513	127,263	120,788
2003	0.506	3,836	3,739	0.515	128,375	120,867
2004	0.509	4,022	3,887	0.515	128,307	120,918
2005	0.512	4,745	4,515	0.513	134,047	127,035
2006	0.507	5,091	4,942	0.516	139,208	130,733
2007	0.510	5,580	5,362	0.514	144,397	136,630
2008	0.513	5,952	5,661	0.514	145,444	137,641
2009	0.521	6,814	6,256	0.514	145,786	137,705
2010	0.521	6,263	5,756	0.511	145,807	139,401
2011	0.521	6,446	5,936	0.514	147,489	139,638
Total	0.515	70,325	66,322	0.514	2,827,761	2,672,706

*For 1979–1991.

Table S7. Birth sex ratios of babies born via by GIFT in Australia and New Zealand between 1985 and 2011

Year	Sex ratio	Males	Females
1985–1991	0.516	2,003	1,881
1992	0.535	549	477
1993	0.518	524	487
1994	0.527	457	410
1995	0.506	325	317
1996	0.544	357	299
1997	0.522	236	216
1998	0.512	148	141
1999	0.504	116	114
2000–2001	0.529	119	106
2002	—	—	
2003	—	—	
2004	0.567	17	13
2005	—	—	
2006	—	—	
2007	—	—	
2008	—	—	
2009	—	—	
2010	—	—	
2011	—	—	
Total	0.521	4,851	4,461

—, no data.

Table S8. PSR estimates from mammals

Species and study	Sex ratio	Males	Females	Sexing method
Cat; Graham (1954) (1)	0.450	9	11	NM
Cat; Austin and Amoroso (1957) (2)	0.483	14	15	NM
Hamster; Sundell (1962) (3)	0.643	63	35	NM
Hamster; Chow et al. (1996) (4)	0.531	51	45	NM
Mouse; Macdowell and Lord (1925, 1926) (5, 6)	0.501	416	415	NM
Mouse; Vickers (1967) (7)	0.500	49	49	NM
Pig; Crew (1925) (8)	0.576	592	436	NM
Pig; Parkes (1925) (9)	0.591	166	115	NM
Pig; Axelson (1968) (10)	0.542	13	11	NM
Rabbit; Melander (1962) (11)	0.509	28	27	NM
Rabbit; Fechheimer and Beatty (1974) (12)	0.486	211	223	NM
Roe Deer; Aitken (1974) (13)	0.514	18	17	NM
Sheep; Henning (1939) (14)	0.509	495	477	NM
Cat; Ciani et al. (2008) (15)	0.568	21	16	M
Cow; Utsumi and Iritani (1993) (16)	0.488	21	22	M
Cow; Hasler et al. (2002) (17)	0.492	1,950	2,014	M
Mouse; Bradbury et al. (1990) (18)	0.558	48	38	M
Mouse; Kunieda et al. (1992) (19)	0.479	34	37	M
Mouse; Byrne et al. (2006) (20)	0.514	247	234	M
Pig; Pomp et al. (1995) (21)	0.536	112	97	M
Sheep; Catt et al. (1997) (22)	0.592	45	31	M
Sheep; Gutiérrez-Adán et al. (1997) (23)	0.500	18	18	M
Sheep; Green et al. (2008) (24)	0.381	8	13	M

M, molecular; NM, nonmolecular.

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Table S9. Age-specific estimates of the sex ratio of the 1900 cohort in the United States

Age, y	Sex ratio	Male	Female	Age, y	Sex ratio	Male	Female	Age, y	Sex ratio	Male	Female
0	0.507	919,000	892,000	35	0.499	919,828	923,875	70	0.430	546,846	725,128
1	0.506	945,000	924,000	36	0.499	917,682	920,743	71	0.426	521,292	702,415
2	0.505	964,000	946,000	37	0.499	915,175	917,354	72	0.420	489,586	675,115
3	0.504	972,000	955,000	38	0.500	913,475	914,880	73	0.415	464,833	655,005
4	0.504	974,000	959,000	39	0.500	911,200	912,647	74	0.408	434,255	631,109
5	0.504	972,000	957,000	40	0.501	912,568	910,642	75	0.400	405,468	608,280
6	0.504	965,000	949,000	41	0.501	912,038	909,471	76	0.392	386,492	599,081
7	0.504	956,000	940,000	42	0.501	910,391	907,147	77	0.384	362,430	582,115
8	0.505	949,000	931,000	43	0.502	910,601	904,809	78	0.382	356,824	578,417
9	0.505	944,000	925,000	44	0.502	909,509	902,868	79	0.373	321,181	538,944
10	0.506	944,000	923,000	45	0.501	910,867	906,472	80	0.361	262,589	465,269
11	0.507	946,000	921,000	46	0.501	906,441	903,237	81	0.350	231,064	429,714
12	0.506	951,000	927,000	47	0.501	898,724	896,378	82	0.346	208,777	395,048
13	0.505	960,000	941,000	48	0.500	887,369	886,839	83	0.336	192,055	378,789
14	0.502	964,000	955,000	49	0.500	874,468	875,479	84	0.326	172,718	356,564
15	0.501	959,000	957,000	50	0.499	863,972	866,456	85	0.317	150,549	323,731
16	0.498	945,000	951,000	51	0.498	865,284	871,306	86	0.308	129,315	290,007
17	0.497	931,000	944,000	52	0.498	854,858	861,998	87	0.299	110,707	259,976
18	0.488	899,000	944,000	53	0.497	831,596	840,521	88	0.289	90,412	222,118
19	0.487	892,000	941,000	54	0.497	816,115	827,159	89	0.275	81,234	214,677
20	0.492	912,000	943,000	55	0.495	810,175	825,897	90	0.262	61,358	172,487
21	0.492	912,000	943,000	56	0.494	799,549	820,515	91	0.251	50,066	149,463
22	0.491	909,000	944,000	57	0.492	793,459	820,901	92	0.240	40,219	127,244
23	0.494	931,000	954,000	58	0.492	803,724	829,370	93	0.228	31,483	106,462
24	0.496	949,000	963,000	59	0.486	766,040	809,007	94	0.219	24,115	86,082
25	0.496	941,000	955,000	60	0.483	736,335	789,493	95	0.209	17,463	66,114
26	0.496	929,000	944,000	61	0.479	708,734	769,803	96	0.198	12,925	52,319
27	0.496	929,000	943,000	62	0.476	686,775	755,702	97	0.191	9,385	39,726
28	0.497	939,000	950,000	63	0.472	669,899	749,115	98	0.184	6,576	29,139
29	0.497	939,000	951,000	64	0.467	656,218	747,776	99	0.189	4,616	19,840
30	0.497	929,367	939,650	65	0.462	641,224	745,983				
31	0.498	927,343	936,201	66	0.456	624,057	744,682				
32	0.498	924,892	932,409	67	0.450	606,110	740,306				
33	0.498	922,718	928,996	68	0.445	583,782	728,696				
34	0.499	921,325	926,446	69	0.440	557,079	709,467				