ABO BLOOD GROUPS AND HUMAN SEX RATIO AT BIRTH

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Summary. In the aggregate of the seventeen published series of the ABO blood groups of newborn babies and their mothers (an aggregate totalling 53,679 mother–baby combinations) there are substantial reciprocal differences by maternal ABO blood group in respect of the ratio of male to female babies. The ratio is relatively low for AB babies of AB mothers plus A babies of A mothers, but is relatively high for non-AB babies of AB mothers plus non-A babies of A mothers. By contrast, the ratio is relatively high for O babies of O mothers plus B babies of B mothers, but (except in the aggregate of seven of the seventeen series, totalling 16,601 cases) is relatively low for non-O babies of O mothers plus non-B babies of B mothers. Disregarding the babies' blood groups, the sex ratio is higher for babies of AB than of non-AB mothers. Disregarding the mothers' blood groups, the sex ratio is lower for A than non-A babies, while in the author's own series, included above, the ratio is lower for A babies possessing than for those not possessing detectable A₁ antigen. It is suggested that a possible cause of these differences is sex-differential fetal mortality caused by interaction of the ABO genes, and some of the sex-determining genes, with oestrogen and progesterone.

INTRODUCTION

In 1925 Hirszfeld & Zborowski reported a series of 264 mother–baby combinations. They pointed out that the ratio of male to female babies was very much higher for the babies of group AB mothers than for the rest, and they declared that “if this finding were confirmed, it would have far-reaching theoretical significance”. Unfortunately, their finding fell immediately into oblivion, but, a third of a century later, it was found to be confirmed (Allan, 1959) in the aggregate, totalling 32,046 cases, of all other series reported between 1924 and 1959 (Dossena, 1924; Badino, 1927; Klasten, 1927; Graff & Werkgartner, 1928; Kirwan-Taylor, 1930; Goroncy, 1930; Haselhorst, 1930; Hurst, Taylor & Wiener, 1946; Sanghvi, 1951; Johnstone, 1954; Cohen & Glass, 1956, 1959; Shield, Kirk & Jakobowicz, 1958; Allan, 1959).

Meanwhile, Sanghvi (1951) had pointed out that, in his own series, the sex ratio was very much higher for O babies of O mothers and, separately, B babies of B mothers, than for A babies of A mothers. This finding too was found

to be confirmed in the aggregate of the other 1924–59 series (Allan, 1959), and there the matter rested for a decade. Since 1970, however, three more series have been reported (Krauss & Zimmermann, 1970; Maráz, Keserü, Kaiser, Annus & Szontágh, 1972; Golovachen & Slozina, 1972), while the author's own series has been substantially enlarged. The resulting new aggregate, totalling 53,679 cases, not only provides overwhelming confirmation of the findings both of Hirszfeld & Zborowski (1925) and of Sanghvi (1951), as is self-evident from the Tables, but has also produced a third finding, complementary to that of Sanghvi, and it is principally this that is dealt with below.

MATERIALS AND METHODS

The author's series consists of 8074 babies born in 1956–59, mostly to Rh-positive mothers, in Aberdeen Maternity Hospital and its associated nursing homes, and 6377 babies born there in 1960–68 to Rh-negative mothers or to Rh-positive mothers with a history of blood transfusion or stillbirth, or of having had a baby with neonatal anaemia or jaundice, including haemolytic disease of the newborn. As in all the other series, stillborn babies and twins were omitted.

The ABO and Rh blood groups of the mothers and babies were determined by standard methods, more than once in the case of Rh-negative mothers and of a substantial minority of Rh-positive mothers. Mothers and babies were recorded as Rh-negative if they lacked the antigen D, whether or not they possessed C or E. The sub-groups of a total of 1338 group A babies were determined with absorbed anti-A₁ serum.

RESULTS

Table 1 gives the data from the author's Aberdeen series. It shows, firstly, that in this series there were substantial differences in sex ratio, by maternal ABO blood group, not only between babies of the same group as their mothers but also between babies of a different group from their mothers. Secondly, it shows that the latter differences were reciprocal to the former. Thus the sex ratio was, as expected, higher for O babies of O mothers, i.e. 1.08 (2713:2508), and for B babies of B mothers, i.e. 1.10 (377:344), than for A babies of A mothers, i.e. 1.00 (1571:1567), χ^2 being 2.75 ($P>0.05$) for the O:A comparison, and 1.07 ($P>0.30$) for the B:A comparison. Conversely, the sex ratio was higher for non-A babies of A mothers, i.e. 1.11 (1030:930), than for non-O babies of O mothers, i.e. 1.02 (1060:1042), and for non-B babies of B mothers, i.e. 0.99 (433:437), χ^2 being 1.75 ($P>0.10$) for the A:O comparison, and 1.76 ($P>0.10$) for the A:B comparison.

Table 1 also shows that babies of AB mothers followed the same trend as babies of A mothers, in respect both of babies of the same group as their mothers and of babies of a different group from their mothers. The data were therefore divided into those concerning the babies of AB plus A mothers, and those for the babies of O plus B mothers.

Table 1. Sex ratio of Aberdeen newborn babies, by their own and their mothers' ABO blood groups

<i>Aberdeen mothers with babies of the same ABO blood group as themselves</i>				<i>Aberdeen mothers of one ABO blood group with babies of other ABO blood groups</i>					
<i>Mothers</i>	<i>Babies</i>	<i>Male babies</i>	<i>Female babies</i>	<i>Male: female</i>	<i>Mothers</i>	<i>Babies</i>	<i>Male babies</i>	<i>Female babies</i>	<i>Male: female</i>
AB	AB	34	33	1.03	AB	A	115	95	1.21
						B	92	70	1.31
A	A	1571	1567	1.00	A	AB	111	104	1.07
						O	833	757	1.10
						B	86	69	1.25
O	O	2713	2508	1.08	O	A	786	760	1.03
						B	274	282	0.97
B	B	377	344	1.10	B	AB	76	81	0.94
						A	94	92	1.02
						O	263	264	1.00
Total		4695	4452	1.05	Total		2730	2574	1.06
AB+A Mothers		1605	1600	1.00	AB+A Mothers		1237	1095	1.13
O+B Mothers		3090	2852	1.08	O+B Mothers		1493	1479	1.01
$\chi^2_{(1)}$		3.01; $P > 0.05$			$\chi^2_{(1)}$		4.02; $P < 0.05$		

Table 2 compares the author's series with the aggregate of the other sixteen series reported in 1924-74, and shows that the Aberdeen results were paralleled in the sixteen-series aggregate. The sex ratio of non-AB babies of AB mothers plus non-A babies of A mothers was high, both in the Aberdeen series, i.e. 1.13 (1237:1095), and in the aggregate, i.e. 1.15 (4146:3596). By contrast, the sex ratio of non-O babies of O mothers plus non-B babies of B mothers was low, both in the Aberdeen series, i.e. 1.01 (1493:1479), and in the aggregate, i.e. 1.05 (4523:4316), χ^2 being 4.02 ($P < 0.05$) in respect of the Aberdeen series and 9.28 ($P < 0.005$) in respect of the aggregate.

In consequence of the immediately foregoing differences being reciprocal to those observed in respect of babies of the same group as their mother, the sex ratio in the aggregate of all seventeen series reported in 1924-74 was higher for O babies of O mothers plus B babies of B mothers, i.e. 1.11 (9832:8819), than for non-O babies of O mothers plus non-B babies of B mothers, i.e. 1.04 (6016:5795), $\chi^2_{(1)}$ being 9.11, and $P < 0.005$. Similarly, the sex ratio was higher for non-AB babies of AB mothers plus non-A babies of A mothers, i.e. 1.15 (5383:4691), than for AB babies of AB mothers plus A babies of A mothers, i.e. 1.01 (6596:6547), $\chi^2_{(1)}$ being 23.96, and $P < 0.0001$.

By contrast, combination of the above categories of baby shows that, in the aggregate of all seventeen series, the sex ratio was almost exactly the same for the total number of babies of AB plus A mothers, i.e. 1.07 (11979:11238), as for the total number of babies of O plus B mothers, i.e. 1.08 (15848:14614). It also shows that the ratio was almost exactly the same for the total number of babies of the same group as their mothers, i.e. 1.07 (16428:15366), as for the total number of babies of a different group from their mothers, i.e. 1.09 (11399:10486).

The above account requires one substantial qualification, in that the relatively low sex ratio of non-O babies of O mothers plus non-B babies of B mothers found in the aggregate of all seventeen series, i.e. 1.04 (6016:5795), was not true of the aggregate of seven of the seventeen series, totalling 16,601 cases (Table 3). On the contrary, the sex ratio of such babies in this sub-aggregate was 1.13 (2227:1972), which was as high as that of non-AB babies of AB mothers plus non-A babies of A mothers in the same sub-aggregate, i.e. 1.12 (1875:1680). For the rest, however, the two sub-aggregates followed the same trend (Table 3).

The difference between these sub-aggregates can be considered from the standpoint not only of mothers but also of babies. Thus, in respect of babies of a different group from their mother (babies for whom the overall sex ratio was 1.07 in both sub-aggregates), the ratio was higher for AB plus B babies in the sub-aggregate of the ten series, i.e. 1.13 (1817:1615) than in that of the seven series, i.e. 1.06 (1226:1155), $\chi^2_{(1)}$ being 1.13, and $P > 0.20$. By contrast, the sex ratio was higher for O plus A babies in the sub-aggregate of the seven series, i.e. 1.15 (2876:2497), than in that of the ten series, i.e. 1.05 (5480:5219), $\chi^2_{(1)}$ being 7.54, and $P < 0.01$.

In the aggregate of all seventeen series the sex ratio was lower for the total number of A babies, i.e. 1.03 (10476:10141), than for the total number of non-A babies, i.e. 1.10 (17351:15711), $\chi^2_{(1)}$ being 6.61, and $P < 0.02$. This low

sex ratio for A babies in general was not, however, characteristic of all four classes of A baby: on the contrary, the ratio was higher for A babies of AB mothers, i.e. 1.31 (618:471), than for A babies of non-AB mothers, i.e. 1.02 (9858:9670), $\chi^2_{(1)}$ being 15.96, and $P < 0.0001$.

Of the 5080 A babies in the Aberdeen series, the sub-groups of 1338 were determined. The A_1 antigen was detected in 333 (24.9%) of these, i.e. in about a third of the percentage of cases in which it was found in Aberdeen school-children (T. M. Allan, unpublished observations). The sex ratio was lower for these 333 babies, i.e. 0.83 (151:182), than for the rest, i.e. 1.08 (523:483), $\chi^2_{(1)}$ being 4.15, and $P < 0.05$.

Table 2. Sex ratio of Aberdeen and other white newborn babies, by their own and their mothers' ABO blood group

ABO blood group		Aberdeen series			Aggregate of all sixteen other series, 1924-74		
Mothers	Babies	Male babies	Female babies	Male: female	Male babies	Female babies	Male: female
AB	A B	207	165	1.25	887	680	1.30
A	AB O B	1030	930	1.11	3259	2916	1.12
O	O	2713	2508	1.08	5540	4949	1.12
B	B	377	344	1.10	1202	1018	1.18
O	A B	1060	1042	1.02	2928	2805	1.04
B	AB O A	433	437	0.99	1595	1511	1.06
AB	AB	34	33	1.03	155	136	1.14
A	A	1571	1567	1.00	4836	4811	1.01
Total		7425	7026	1.06	20402	18826	1.08
$\chi^2_{(7)}$		8.59; $P > 0.20$			37.91; $P < 0.0001$		
AB + A Mothers		2842	2695	1.05	9137	8543	1.07
O + B Mothers		4583	4331	1.06	11265	10283	1.10
Mothers + babies of the same group		4695	4452	1.05	11733	10914	1.08
Mothers + babies of different group		2730	2574	1.06	8669	7912	1.10

DISCUSSION

The aggregate data presented above make it virtually certain that there are differences in the ratio of male to female newborn babies in relation to ABO blood group. In respect of individual blood groups, the two most notable differences are, firstly, a higher sex ratio for babies of AB mothers (1.27) than for the rest (1.07), and, secondly, a lower sex ratio for A babies (1.03) than for the rest (1.10). These two differences, however, fall within an apparently systematic framework of differences involving mothers and babies of all four groups, in two reciprocal combinations. Thus babies born to mothers of blood groups AB and A combined, i.e. babies born to mothers who possess at least one A gene, A individuals being of the genotype AA or AO , have, in this aggregate, a relatively high sex ratio (1.15) when of a different group from their mothers,

and a relatively low sex ratio (1.01) when of the same group as their mothers. Conversely, babies born to mothers of blood groups O and B combined, i.e. babies born to mothers who lack the *A* gene, have, in this aggregate, a relatively high sex ratio (1.11) when of the same group as their mothers, and a relatively low sex ratio (1.04) when of a different group from their mothers. This reciprocity is such that, when the data for the two types of baby contrasted above are combined, the sex ratio is found to be almost exactly the same for babies of the total number of AB plus A mothers (1.07) as for babies of the total number of O plus B mothers (1.08), and almost exactly the same for the total number of babies of the same group as their mothers (1.07) as for the total number of babies of a different group from their mothers (1.09).

This reciprocity recalls the theory of Ford (1942), endorsed by Huxley (1955), that the *ABO* blood-group genes are an example of balanced polymorphism, i.e. of a genetic system maintained by means of a balance between opposed selective forces, these being themselves nearly always genetic. More particularly, it recalls the model of Owen (1953), consisting of "a genetical system admitting of two distinct stable equilibria under natural selection". Models appropriate to the more complicated balance described above would, however, be far more complex (W. F. Bodmer, personal communication). Moreover to this complexity must be added the complicating factor of the high sex ratio for non-O babies of O mothers plus non-B babies of B mothers found in the aggregate of seven of the seventeen series. This variation may be due to chance, may be a characteristic of the particular populations represented in the seven series concerned, or may be a result of the samples differing in, for example, the proportions of primiparae and multiparae, or the proportions of mothers included more than once.

The data appear to provide no clue as to the particular form which genetic forces, balanced or otherwise, might take in the present context, there being no evidence that the differences found are related to *ABO* compatibility and incompatibility, to *ABO* homozygosity and heterozygosity, or, with the possible exception of A mothers of A babies, to whether the mother is Rh-positive or Rh-negative (T. M. Allan, unpublished observations). Consideration will therefore be given to two theoretical possibilities.

The first of these, suggested by E. B. Ford (personal communication), is that the differences found are due to sex-differential fertilization, resulting from some form of interaction between the *ABO* blood-group genes and the genes which determine the relative frequencies of the X- and Y-bearing gametes. The statement of Cavalli-Sforza & Bodmer (1971) that gametic selection may act in the opposite direction to zygotic selection is complementary to this suggestion, in that, for example, "a gene whose effect is detrimental to zygotes may be selected for in gametes, and a polymorphism may then result when these two opposing forces balance each other". There is, however, no convincing evidence of haploid spermatic expression of the *ABO* genes (Race & Sanger, 1968); and indeed, as Cavalli-Sforza & Bodmer (1971) point out, the whole problem of proving the existence of prezygotic selection is "unsolved, perhaps even insoluble".

The second possibility, suggested by Allan (1972), is that the differences are

Table 3. Sex ratio of white newborn babies, by their own and their mothers' ABO blood groups, and by series

ABO blood group		Combined series (I)*				Combined series (II)†			
Mothers	Babies	Male babies	Female babies	Total male babies	Total female babies	Male babies	Female babies	Total male babies	Total female babies
AB	A	382	291	696	514	1-35	236	180	331
	B	314	223			162	151		
A	AB	304	260	2812	2497	1-13	176	183	1349
	O	2208	1985			1003	887		
B	B	300	252			298	279		
O	O	6241	5564	7274	6453	1-13	2012	1893	2366
B	B	1033	889			546	473		
AB	AB	121	110	4671	4549	1-03	68	59	1925
A	A	4550	4439			1857	1939		
O	A	1948	1922	2595	2580	1-01	975	864	1393
	B	647	658			418	403		
B	AB	252	222	1194	1243	0-96	172	139	834
	A	259	305			269	201		
	O	683	716			393	365		
Total		19242	17836	19242	17836	1-08	8585	8016	8585
									8016
									1-07

* Data from Hirsfeld & Zborowski (1925); Badino (1927); Graff & Werkgartner (1928); Kirwan-Taylor (1930); Goroncy (1930); Haselhorst (1930); Sanghvi (1951); Shield *et al.* (1958); Maráz *et al.* (1972); Allan (1972).
† Data from Dossena (1924); Klaffen (1927); Hurst *et al.* (1946); Johnstone (1954); Cohen & Glass (1956, 1959); Krauss & Zimmerman (1970); Golovachen & Slozina (1972).

due to sex-differential fetal mortality, resulting from interaction between the *ABO* blood-group genes and some of the genes determining sex, the interaction being regulated by oestrogen and progesterone, perhaps through a 'threshold dichotomy' (Wright, 1968). This possibility is supported circumstantially by six sets of findings. The first is that one of the precursors of oestrogen and progesterone is cholesterol; that placental biosynthesis of progesterone is affected by fetal sex (Hagemenas & Kittinger, 1974); and that a slightly raised mean level of serum cholesterol is characteristic of blood-group A (Mayo, Fraser & Stamatoyannopoulos, 1969). The second is that the association between blood-group A and venous thrombo-embolism (Dick, Schneider, Brockmüller & Mayer, 1963) is stronger in pregnant or puerperal women than in medical or surgical patients, and is probably even stronger in cases associated with oral contraception (Mourant, Kopeć & Domaniewska-Sobczak, 1971), in which both oestrogen and progesterone are crucial, and in which the serum cholesterol level is raised (Stokes & Wynn, 1971). The third is that other conditions associated with blood-group A are superficial puerperal thrombophlebitis (Allan & Stewart, 1971) and gynaecological cancer (Helmbold, 1961; Garriga & Ghossein, 1963; Miluničová, Jandová & Škoda, 1971), including cancer of the breast in middle-aged but not in older women (Hems, 1970), and that, in gynaecological cancer, both oestrogen and progesterone are factors of such importance as to have prompted a blood-group survey of response to therapeutic ovariectomy in cancer of the breast (Lee, 1971). The fourth is that pregnant mice fed on a diet grossly deficient in essential fatty acids (EFA) lose about two thirds of the male fetuses (Rivers & Crawford, 1974), and that adult male mice have a high EFA requirement which is presumed to be related to the known effects of oestrogen on EFA metabolism (Lyman, 1968). The fifth is that administration of oestrogen and progesterone to rats in the earliest stages of pregnancy markedly raises the sex ratio of live fetuses of non-ovariectomized subjects through excess female fetal mortality, and markedly lowers the sex ratio of live fetuses of ovariectomized subjects through excess male fetal mortality, the mean litter size being greatly reduced in both cases (Hahn & Hayes, 1963). The sixth is that the sex ratio is markedly raised (without effect on litter size) by injection of non-specific anti-oestradiol antibody into rats for the first 4 days after mating (Wotiz, Scublinsky & Walker, 1972).

The first three of these six sets of findings—those on cholesterol, thrombo-embolism and gynaecological cancer—suggest that interaction of the *ABO* genes with oestrogen and progesterone must be considered a possibility, in more than one field, while the finding on EFA in pregnant mice suggests that oestrogen can affect sex ratio indirectly, and the various findings in pregnant rats prove that oestrogen and progesterone can affect sex ratio directly. A possible site of interaction between these hormones and the *ABO* blood-group genes would be the receptors of the hormones since, if the receptors are glycoproteins, they may have polysaccharide side-chains with either ABO or related specificities (W. F. Bodmer, personal communication), and there is evidence that the oestrogen-receptor association may precede genetic transcription and translation (McGuire & Lisk, 1971; Hamilton, Teng, Means & Luck, 1971).

Other agents which should possibly be considered in this connection are testosterone, HCG, prostaglandins, ACTH and histocompatibility genes. Whatever the mechanisms, however, which may actually be in force, an indication of whether the differences observed are the result of sex-differential fetal mortality or of sex-differential selection at an earlier stage, or both, might well be obtained from large-scale blood grouping and sexing, chromosomal or nuclear, of induced and spontaneous abortuses alike (F. E. Hytten, personal communication). Such studies would have to be performed in the light of the great variety of factors, environmental and genetic, from the prezygotic stage onwards, which are already known to contribute to sex-differential fetal mortality (for references see Geiringer, 1961; Stevenson & Bobrow, 1967; Hytten & Leitch, 1971), and also in the light of three complementary sets of evidence on fetal sex ratio in general. The first is the long-standing evidence that in the later stages of pregnancy, there is an excess of male fetal mortality. The second is the accumulating evidence that in the early weeks of pregnancy there is either approximate sex equality in fetal mortality (Tietze, 1948; Bochkov & Kostrova, 1973) or an excess of female fetal mortality (Mikamo, 1969). The third is the substantial recent evidence (Kaufman, 1973; Fechheimer & Beatty, 1974) that the mammalian sex ratio at conception is very close to 1.00.

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