

# HETEROSPECIFIC PREGNANCY

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Hirsfeld (1928) was the first to draw attention to the numbers of children of each ABO blood group born of various mating types, and reported fewer Group A children born of A × O matings (56·6 per cent.) than of O × A matings (63·8 per cent.). He later reviewed data gathered between 1927 and 1933 but was unable to confirm his previous findings (Hirsfeld, 1934).

However the position was re-investigated by Waterhouse and Hogben (1947), who pooled the family blood group data of twelve authors and showed that only 56·1 per cent. Group A children were born of A × O matings compared with 61·7 per cent. born of O × A matings. They claimed there to be a deficiency of 25 per cent. of Group A children in A × O matings, which represents a foetal mortality of 8 per cent. of Group A foetus, or about 3 per cent. of all conceptions. To explain this, it was suggested that the anti-A agglutinin of Group O mothers reacted adversely with their Group A foetus to produce early and late foetal deaths.

This same suggestion had been advanced by Levine (1943) in explanation of certain abortions; he claimed that women of heterospecific matings had a higher abortion rate than those of homospecific matings.

This paper presents a further investigation of the problem, the object being to determine whether or not the fact that a mating is heterospecific has any bearing on the number of children of each blood group born of it.

## MATERIAL

In the period November, 1949, to December, 1950, blood samples were obtained from mothers delivered in this hospital, from their infants, and from the infants' fathers. The ABO and Rh groups of the samples were determined by the tube technique described in Medical Research Council Memoranda No. 9 (1943) and No. 19

(Mollison and others, 1948). Details of previous pregnancies were recorded, but it was not possible to examine any previous children. All live-born infants, irrespective of the period of gestation, were included in this sample; no still-births were included.

There was no deliberate selection of cases, every endeavour being made to secure samples from each mother, father, and child throughout the period of investigation.

## DEFINITIONS

When the red cells of the father or child possess an antigen which can be agglutinated by the anti-A or anti-B agglutinin of the mother's serum (*i.e.* an antigen not possessed by the mother), the mating or pregnancy is considered heterospecific or incompatible, in contrast with a homospecific or compatible mating or pregnancy in which no such antagonism can exist (Levine, 1943; Table I).

TABLE I  
BLOOD GROUPS OF MOTHER, FATHER, AND CHILD IN HOMO- AND HETEROSPECIFIC PREGNANCIES AND MATINGS

Blood Group of Mother	Blood Group of Child		Blood Group of Father	
	Homo-specific	Hetero-specific	Homo-specific	Hetero-specific
O	O	A, B	O	A, B, AB
A	O, A	B, AB	O, A	B, AB
B	O, B	A, AB	O, B	A, AB
AB	A, B, AB	—	O, A, B, AB	—

While the mating Father A × Mother O is classified as heterospecific, not all of the resulting pregnancies are to be so regarded. Should the father be of the genotype AO, half of the children are likely to be of Group O; where this is so the pregnancy is homospecific, but where the child is Group A the pregnancy is heterospecific.

When dealing with the Rh system, only Rh-negative mothers with Rh-positive children and husbands have been considered to be heterospecific pregnancies and matings, as the elementary Rh antigens *c*, *d*, and *e* act as very weak antigens normally.

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Matings will always be shown with the group of the father first, *i.e.* O × A represents a father of Group O and a mother of Group A.

RESULTS

ABO MATINGS.—The ABO blood group of 2,578 families (5,156 adults and 2,596 children) was determined, and the gene frequencies of the sample, calculated by Fisher's method (Dobson and Ikin, 1946), are set out in Table II. Comparison of the expected (264) and observed (241) numbers of Group AB persons serves as a check on the randomness of the sample ( $\chi^2=1.375$ ;  $P>0.20 <0.30$ ).

TABLE II  
GENE FREQUENCIES OF 5,156 ADULTS AND 2,596 CHILDREN

Gene	Adults	Children	Adults and Children
O	0.67137	0.66576	0.66949
A	0.26589	0.26880	0.26686
B	0.06273	0.06543	0.06364

The expected numbers of children of each blood group born of each mating type were calculated from formulae given by Waterhouse and Hogben (1947); they are compared with the observed numbers in Table III. Seventeen children have blood groups inconsistent with those of their alleged parents. It was not possible to re-examine all of these discrepancies, but where this was done doubt about the alleged father was usually revealed; in accordance with general experience most of these

were first pregnancies. In a few instances mislabelling of specimens may have occurred, but great trouble was taken to exclude this by careful checking. Comparison of the expected and observed numbers of children by the  $\chi^2$  test show a significant difference between the two figures only in the matings O × A and B × A.

The reciprocal matings O × A and A × O will be considered in detail as they comprise the largest number, and the findings in these types may be compared with those of previous authors.

If, in A × O matings, as suggested by Waterhouse and Hogben (1947), the anti-A agglutinin in the Group O mother's serum is capable of acting lethally, either early or late in pregnancy on any group A foetus which she may carry, then fewer Group A children may be born of these matings than of O × A matings. From Table IV this indeed seems to be the case; this agrees with the reports of Hirsfeld (1928) and of Waterhouse and Hogben (1947) which are given here for comparison. However, when the total numbers, and not merely the

TABLE IV  
PERCENTAGE OF GROUP A CHILDREN BORN OF O × A AND A × O MATINGS

Series	Percentage of Group A Children		Difference
	Mating O × A	Mating A × O	
Present . . . .	62.6 ± 1.55	58.2 ± 1.59	4.4 ± 2.19
Hirsfeld (1928) . .	63.8 ± 1.36	56.6 ± 1.36	7.2 ± 1.92
Waterhouse and Hogben (1947)	61.7 ± 1.7	56.1 ± 1.9	5.6 ± 2.54

TABLE III  
OBSERVED AND EXPECTED NUMBERS OF CHILDREN OF EACH GROUP BORN OF EACH MATING TYPE COMPARED, USING THE  $\chi^2$  TEST

Mating		Number of Matings	Group of Children								Number of Children	$\chi^2$	Degrees of Freedom	P
Father	Mother		O		A		B		AB					
		Ex-pected	Ob-served	Ex-pected	Ob-served	Ex-pected	Ob-served	Ex-pected	Ob-served					
O	O	550	555	546	—	8*	—	1*	—	—	555	—	—	—
A	O	471	198	197	276	276	—	1*	—	—	474	0.005	1	0.9
B	O	112	55	59	—	—	60	55	—	—	114	0.711	1	0.5
AB	O	33	—	1*	17	14	17	18	—	1*	34	0.470	1	0.5
O	A	485	203	181	284	305	—	1*	—	—	487	3.904	1	< 0.5
A	A	500	88	79	416	425	—	—	—	—	504	1.114	1	0.3
B	A	99	20	20	28	20	22	33	30	26	99	8.729	3	< 0.5
AB	A	32	—	1*	16	16	7	9	9	6	32	1.587	2	0.5
O	B	99	47	48	—	1*	52	50	—	—	99	0.091	1	0.8
A	B	90	18	20	25	18	20	20	28	33	91	3.074	3	0.5
B	B	18	4	—	—	—	14	17	—	—	18	2.892	1	0.1
AB	B	11	—	1*	3	1	6	5	3	4	11	0.733	2	0.7
O	AB	31	—	—	16	15	16	15	—	1*	31	0.000	1	—
A	AB	35	—	—	18	18	7	7	10	10	35	0.000	2	—
B	AB	9	—	—	2	2	5	5	3	2	9	0.155	2	0.9
AB	AB	3	—	—	1	1	1	1	2	1	3	0.999	2	0.7
Total	..	2,578	1,188	1,154	1,102	1,120	227	238	85	84	2,596	2.142	3	0.5
											$\Sigma \chi^2$	24.564	24	0.5

\* Exceptions to Bernstein's law.

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TABLE V  
EXPECTED AND OBSERVED NUMBERS OF CHILDREN BORN OF O × A AND A × O MATINGS COMPARED,  
USING  $\chi^2$  TEST (EXCEPTIONS TO BERNSTEIN'S LAW EXCLUDED)

Series	Mating		Number of Children	Group of Children				$\chi^2$	P
	Father	Mother		O		A			
				Expected	Observed	Expected	Observed		
Present	O	A	487	203	181	284	305	3.904	<0.05
	A	O	474	198	197	276	276	0.005	0.9
Hirszfeld (1928)	O	A	570	236	202	334	364	7.404	<0.01
	A	O	606	251	257	355	343	0.650	0.5
Waterhouse and Hogben (1947)	O	A	835	349	320	486	515	4.139	<0.05
	A	O	686	287	301	399	385	1.173	0.3

TABLE VIA  
NUMBER OF CHILDREN OF EACH GROUP IN EACH BIRTH RANK

Mating		Group of Children	Birth Rank of Children											Total
Father	Mother		1	2	3	4	5	6	7	8	9	10	11	
O	A	A	139	104	29	20	6	1	2	2	1	1	—	305
		O	85	58	22	10	4	1	1	—	—	—	—	181
A	O	A	130	100	34	5	3	4	—	—	—	—	—	276
		O	100	66	20	6	2	2	—	—	—	—	1	197

percentages of children born of these matings, are considered (Table III) another aspect of the problem emerges. It is in the heterospecific A × O matings that the expected and observed numbers of children of each group fit most closely, while in the homo-specific O × A matings there is a significant deviation, with a deficiency of Group O children, the observed number being actually 22 less than expected.

This is the only mating of any magnitude in the whole sample which shows a significant difference between the expected and observed numbers of children of each blood group.

This finding being unexpected, the data of Hirszfeld (1928) and of Waterhouse and Hogben (1947) were recalculated and similar significant results were obtained in each instance (Table V).

Waterhouse and Hogben (1947) found that the A/O ratio of children born of A × O matings decreased with birth rank, particularly from the third rank onwards, and they presumed that this might be due to an increase in the maternal anti-A titre with repeated heterospecific pregnancies. No such decrease was found in this sample (Table VIA and B), but the total numbers from the third rank onwards are small, and, under present-day conditions, an enormous population sample would require to be tested in order to obtain a satisfactory series and yet avoid selection of appropriate families.

TABLE VIB  
A/O RATIO BY BIRTH RANK

Mating		A/O Ratio by Birth Rank		
Father	Mother	1	2	3 and all others
O	A	1.63	1.79	1.63
A	O	1.30	1.51	1.48

In this series very similar figures were obtained for the A/O ratio in each pregnancy rank.

Again, assuming heterospecific pregnancy to be capable of producing an undue proportion of foetal deaths, fewer women in A × O matings would be expected to proceed to term and be delivered of viable infants, than in O × A matings. That this is not so is obvious from Table VII, in which the numbers of mothers delivered of viable infants of the two matings under consideration are shown.

TABLE VII  
NUMBERS OF O × A AND A × O MATINGS IN WHICH THE MOTHER WAS DELIVERED OF A LIVE CHILD

Mating		Percentage of all Matings	Number of Matings		$\chi^2$	P
Father	Mother		Observed	Expected		
A	O	18.3 ± 1.2	471	478	0.205	0.7
O	A	18.8 ± 1.2	485	478		

Similarly, for the whole sample, there is no significant deficit of women in heterospecific matings successfully delivered of a viable infant (Table VIII).

TABLE VIII  
NUMBERS OF HOMO- AND HETEROSPECIFIC  
MATINGS IN ENTIRE SAMPLE

Mating Type	Total Numbers	Percentage	Percentage expected in a random sample
Homospecific	1,730	67·1	66
Heterospecific	848	32·9	34

Although the  $O \times A$  and  $A \times O$  matings are mainly under consideration, any action of the maternal anti-A agglutinin of Group O mothers in  $A \times O$  matings on Group A foetus might equally well be operative in other heterospecific matings such as  $AB \times O$ , and in certain  $A \times B$  and  $AB \times B$  matings, and the total observed number of Group A children in the sample might be significantly less than the expected number. However, reference to Table III shows that these two figures for the whole sample agree very closely and that no deficit of Group A children does exist in the entire sample.

ABO AND RH MATINGS.—In 1,590 of the 2,578 families already analysed, both the ABO and Rh blood groups were determined, giving a total of 3,180 adults and 1,602 children. The gene frequencies are detailed in Table IX. The expected numbers of children born of each Rh mating type have been calculated and are shown, together with the observed

TABLE IX  
RH GENE FREQUENCIES OF THE SAMPLE  
(3,180 ADULTS, 1,602 CHILDREN)

Gene for	Adults	Children	Adults and Children
Rh positive	0·5682	0·5857	0·5740
Rh negative	0·4318	0·4143	0·4260

TABLE X  
EXPECTED AND OBSERVED NUMBERS OF CHILDREN OF THE FOUR Rh MATING TYPES

Rh Type		Number of Matings	Children				Total Number of Children	Degrees of Freedom	$\chi^2$	P
Father	Mother		Positive		Negative					
			Expected	Observed	Expected	Observed				
Positive	Negative	230	163	172	70	61	233	1	1·653	0·3
Negative	Positive	245	173	188	75	60	248	1	4·300	<0·05
Positive	Positive	1,056	965	961	97	101	1,062	1	0·181	0·7
Negative	Negative	59	—	6	59	53	59	—	—	—
Total	.. .. .	1,590	1,301	1,327	301	275	1,602	1	2·764	0·1

numbers, in Table X. The Rh groups of six children in the mating Rh neg.  $\times$  Rh neg. fail to fit with that of their parents.

Again taking the reciprocal matings  $O \times A$  and  $A \times O$ , as they contain the greatest numbers, the expected numbers of children born have been calculated, both the ABO and Rh status of the matings being considered. These figures, together with the observed numbers, are detailed in Table XI (opposite).

No significant deviation is noted between the observed and expected numbers of children born of each mating type, and the sum of  $\chi^2$  tests is only 13·256 ( $P > 0·80 < 0·90$ ). Comparison of the observed and expected numbers of children born of these two matings in this sample, considering only the ABO blood groups, showed no significant deviation.

From this one sample it would appear that the Rh status of the parents in  $O \times A$  and  $A \times O$  matings has no influence on the numbers of children of Groups O and A born of them, provided that cases of maternal Rh iso-immunization are excluded.

MATINGS RESULTING IN ABORTIONS.—Waterhouse and Hogben (1947), claiming a deficit of Group A children born of  $A \times O$  matings, thought this due to the action of the maternal anti-A agglutinin causing an excessive number of early and late foetal deaths. A similar view was propounded by Levine (1943) and also by Wiener and others (1949), who found that, in matings in which two or more abortions had occurred, there was an unduly high proportion of heterospecific matings. Race and Sanger (1950) give the figures for each type of mating expected to be found in a normal random sample of the English population as 66 per cent. homospecific and 34 per cent. heterospecific, with very comparable values for an American population. In the present sample, far from there being an excess of heterospecific matings in the group which have had previous abortions, there are actually rather fewer than would be

TABLE XI  
EXPECTED AND OBSERVED NUMBERS OF CHILDREN OF EACH ABO AND Rh GROUP  
BORN OF O × A AND A × O MATINGS

Mating		Number of Matings	Children								Total Number of Children	Degrees of Freedom	$\chi^2$	P
Father	Mother		A Positive		A Negative		O Positive		O Negative					
			Ex-pected	Ob-served	Ex-pected	Ob-served	Ex-pected	Ob-served	Ex-pected	Ob-served				
O Positive	A Positive	173	92	96	9	7	66	63	7	8	174	3	0.895	0.9
O Negative	A Positive	62	25	31	11	9	18	16	8	6	62	3	2.525	0.5
O Positive	A Negative	54	22	20	10	10	16	17	7	8	55	3	0.386	0.9
O Negative	A Negative	10	—	—	6	8	—	—	4	2	10	1	1.666	0.2
A Positive	O Positive	195	104	101	11	16	74	71	8	8	196	3	3.121	0.5
A Negative	O Positive	44	18	20	8	7	13	12	5	5	44	3	0.424	0.9
A Positive	O Negative	41	17	12	7	8	12	17	5	4	41	3	3.896	0.3
A Negative	O Negative	12	—	—	7	6	—	—	5	6	12	1	0.343	0.7
Total	.. .. .	591	278	280	69	71	199	196	49	47	594	3	0.194	0.9
												$\Sigma\chi^2$	13.256	0.9

expected in a random English population sample. This agrees closely with the data given in the majority of papers dealing with this question (Table XII).

TABLE XII  
PERCENTAGE OF HETEROSPECIFIC MATINGS IN WHICH ABORTIONS HAVE OCCURRED

Series	Number of Abortions	Percentage of Matings		Number of Matings
		Homo-specific	Hetero-specific	
English Random Population ..	—	66	34	—
Levine (1943) ..	2 or more	46	54	115
Wiener, Wexler, and Hurst (1949) ..	2 or more	47	53	89
Race and Sanger (1950)	average of 3	72	28	43
Sjöstedt, Grubb, and Linell (1951) ..	2 or more	64	36	242
Present series ..	2 or more	71	29	48
Present series ..	1 or more	74	26	258

DISCUSSION

Assuming an adverse and probably lethal action on the foetus by the maternal natural agglutinins in heterospecific pregnancies, various effects might be observed:

- (i) fewer children of Group A might be born of the heterospecific A × O matings than of the homo-specific O × A matings;
- (ii) the A/O ratio of children born of the A × O matings might decrease with birth rank while remaining constant in O × A matings;

- (iii) fewer women in A × O matings might proceed to term than of O × A matings;
- (iv) an overall deficit of Group A children might be seen in any population sampled.

Further, in a group of matings in which abortions have occurred, an undue proportion of hetero-specific matings might be observed. These points have all been considered in this work but the results of the investigation do not support any of these assumptions.

In a series of 2,000 mothers and their infants analysed by Boorman (1950) there was no significant deficit of Group A children born of Group O mothers compared with the Group O children born of Group O mothers. A similar observation was reported by Bryce and others (1950). Struthers (1951) suggested that, if there is no deficiency of Group A children to be observed at birth but such a deficiency is found in later life, then this may be due to a selective loss of Group A infants and children. He showed that in his four hundred autopsies there was a deficit of Group O infants and children in the group dying with bronchopneumonia, particularly in those below 2 years of age, and he postulated an increased susceptibility of Group A, B, and AB infants and children to pulmonary infection as a late result of heterospecific pregnancy. However, no parental blood group data were available and his ABO determinations were made by the "slide" technique which is prone to give false results, particularly false positives in infective conditions, especially when blood obtained *post mortem* is used.

Kirk and others (1953), examining a West Australian population, suggested that the fertility of Group O women in compatible matings is greater than that of Group O women in incompatible matings and that of Group A women generally.

Allan (1953), in his analysis of the data of Waterhouse and Hogben (1947), found evidence which suggested that the deficit of Group A children of A × O matings was part of a general shortage of children of all Group A fathers, whatever the mating, rather than the result of any action of the maternal anti-A agglutinin, the average number of children of homospecific and heterospecific matings being found to be remarkably close.

Nevertheless, from their data, Waterhouse and Hogben (1947) calculated there to be a deficiency of 25 per cent. of Group A children born of A × O matings, representing a foetal mortality of 8 per cent. in Group A children, approximately 3 per cent. of all conceptions. This is a very large figure and would considerably alter the ABO gene frequencies of a population in a few generations, provided that the population was not otherwise affected by any great numbers of immigrants, and that no other counterbalancing factor operated. The very large blood-donor samples analysed by Hart (1943) and Roberts (1948) show close agreement between every age group and would suggest that the gene frequencies do indeed remain fairly constant.

The figures given in Table XII suggest that, should there be a loss of Group A children of heterospecific matings, it cannot be accounted for by an excessive number of abortions resulting from such matings. This is not an isolated finding but confirms the reports of various other authors (Hirszfeld, 1949; Race and Sanger, 1950; van Loghem and others, 1950; Sjöstedt and others, 1951). Similarly, AB iso-immunization of the mother is unlikely to account for the loss of many infants, as, despite the increasing numbers of instances reported in the literature, notably those of Boorman and others (1949) and Mollison and Cutbush (1949), such well-authenticated cases are uncommon. Of 3,070 deliveries personally examined, none showed unequivocal evidence of AB iso-immunization compared with an incidence for Rh iso-immunization of approximately one in two hundred.

It is true that the percentage of Group A children born of A × O matings is lower than that born of O × A matings, both in the present sample and in the series of Hirszfeld (1928) and Waterhouse and Hogben (1947), but it appears that this consideration of percentage alone has helped to give rise to the view that there is an actual deficit of Group A

children of A × O matings. When the observed and expected numbers of children of each blood group born of the reciprocal O × A and A × O matings are studied, no significant difference is seen to exist between the two values for the heterospecific A × O matings in any of the three populations studied (Table V). It is in the homospecific O × A matings that a significant difference is observed between the expected and observed numbers of children of each blood group. Such a difference occurring in one sample alone might well be attributed to chance, but its occurrence in three populations is striking. In each instance this difference appears to arise from a deficit of Group O children of the O × A matings, but it is difficult to give any satisfactory reason to account for this.

Differential fertilization of the ovum is unlikely to be a factor. Waterhouse and Hogben (1947) rightly pointed out that the formulae used for the calculation of the expected numbers of children of each blood group born of each mating type depend for their accuracy on the equal viability of the blood group genes. Reference to Table III shows that the genes do appear to have equal viability and that the formulae used appear to be correct, for in nearly every instance the expected and observed numbers of children agree closely; support is afforded to this by the studies of Hart (1943) and Roberts (1948) already mentioned. Similarly, differential foetal mortality *in utero*, unless occurring very early and being mistaken perhaps for a delayed period, is improbable, and, despite this interesting but inexplicable deficit of Group O children of O × A matings (the only mating of any consequence numerically which shows a significant deviation between the observed and expected numbers of children born) the total numbers of observed and expected children of Groups O and A born of all mating types in this sample show remarkably close agreement.

It is suggested that the belief that there is a significant deficit of Group A children born of A × O matings is erroneous, and that this view has arisen largely from considering the relative percentages of children in each blood group born of each mating type instead of considering absolute numbers, and that there is in fact a deficit of Group O children born of O × A matings. Also it has been shown that, in this sample, the total observed number of children of each group born of all mating types agrees very closely with the expected number. It is believed therefore that the maternal natural agglutinins play a very minor role, if any, in determining the number of children of each blood group to be born of the various mating types in a population.

## SUMMARY

(1) Hirszfeld (1928) and Waterhouse and Hogben (1947) found a lower percentage of Group A children born of the heterospecific  $A \times O$  mating than were born of the homospecific  $O \times A$  mating. This problem has been investigated in a sample of the West London and West Middlesex population.

(2) The ABO blood groups of 2,578 families (5,156 adults and 2,596 children) were determined.

(3) The percentage of Group A children born of the  $A \times O$  and  $O \times A$  matings was 58.2 and 62.6 per cent. respectively.

(4) The expected and observed numbers of children of each group agreed closely in the heterospecific  $A \times O$  mating, but differed significantly in the homospecific  $O \times A$  mating. This difference is thought to be due to a deficit of Group O children.

(5) The A/O ratio of children born of the  $A \times O$  mating did not decrease with birth rank, and there was no deficit of mothers of  $A \times O$  matings delivered of a live child, nor of Group A children in the entire sample.

(6) No excess of heterospecific matings was found in a group of matings in which abortions had occurred.

(7) The Rh groups of 1,590 families were determined. The Rh status of the parents exerted no influence on the numbers of children of Groups O and A born of  $A \times O$  and  $O \times A$  matings.

(8) Apart from rare instances of maternal AB iso-immunization, it is believed that the ABO group of the parents and the maternal natural agglutinins

exert little or no effect on the numbers of children of each ABO group born of the various mating types.

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