

## Fertility and Multiple Births\*

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The treatment of female sterility by means of FSH may produce either single or twin or higher multiple births, according to the quantity of administered hormone. Such a possibility seems to indicate the existence of a biological *continuum* between single, twin, and higher multiple births. This is why we planned to study the relations between fertility and multiparity of women.

As geneticists we are inclined to distinguish a genotypical fertility and a phenotypical one; in other words the potential fertility inherited by the woman and the actual fertility formed by the number of children she has born.

Genotypical fertility is also possessed by virgins, while phenotypical one is conditioned by all the influential causes determined by sexual relations and other environmental factors, including the intentional control of fertility.

It follows that phenotypical fertility cannot easily be taken for genotypical one. For example, if we want to compare the genotypical fertility of mothers of singletons to that of mothers of twins, we cannot solve this problem by means of direct comparison of phenotypical fertility between the two classes of mothers, since two equivalent samples are hard to be established.

Therefore we looked for criteria of indirect comparison by means of the following researches:

1) Study of statistical comparisons between single and twin births based on Italian Vital Statistics (ISTAT);

2) Study of the frequency of abortions by mothers of singletons and mothers of twins, based on data obtained from the Obstetrical Clinic of the Rome University;

3) Study of statistical comparisons between single and MZ twin births based on data from the “Gemelloteca”, i.e. the Twin Register of the Mendel Institute in Rome.

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### Research 1

Basing ourselves on ISTAT data, we have considered the distribution of single birth frequencies by maternal age.

From these data it is possible to draw the well known curve which shows the biological fertility of Italian women (Fig. 1); similarly we have considered the frequencies of multiple births by Italian women and drawn the respective curve (Fig. 2).

Subsequently we have equalized the curve of multiple births to that of single births obtaining a curve which we deem interesting (Fig. 3).

In fact the equalized curve shows that for maternal ages 15-29 the frequency of

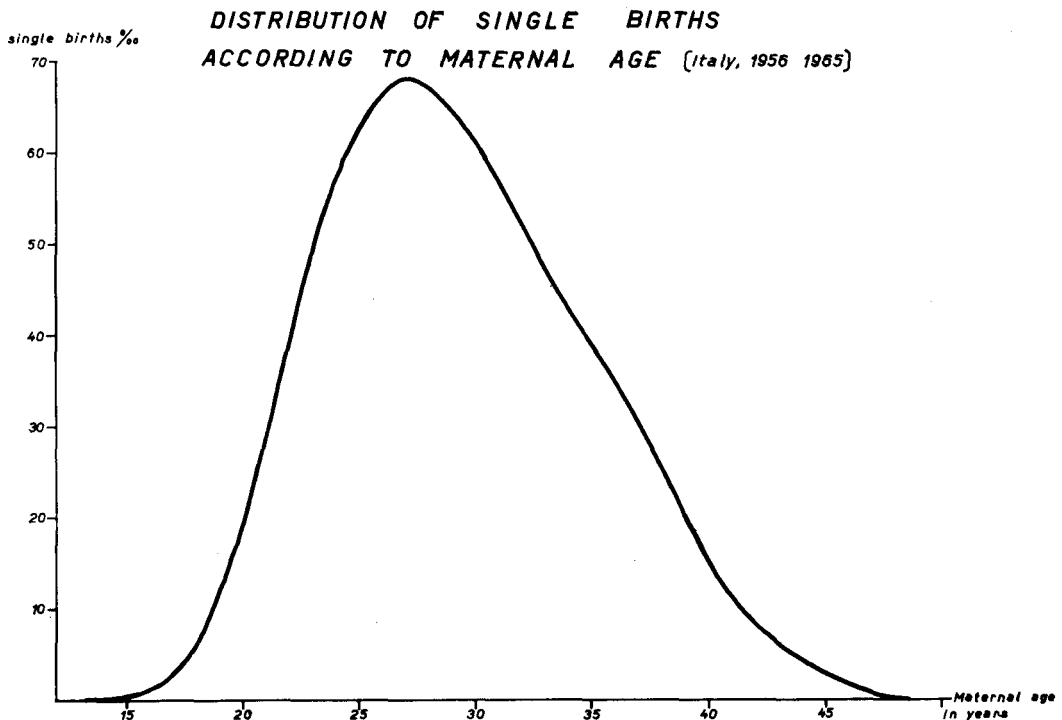


Fig. 1

multiple births appears to be reduced as compared to that of single births, with its negative peak in correspondence with the 23rd year of age. From the 29th to the 43rd year of age the comparative frequency of twin births increases and then decreases reaching its peak at the level of the 36th year of age. Beyond the 43rd year, the frequency of twin births shows no significant difference from that of single births.

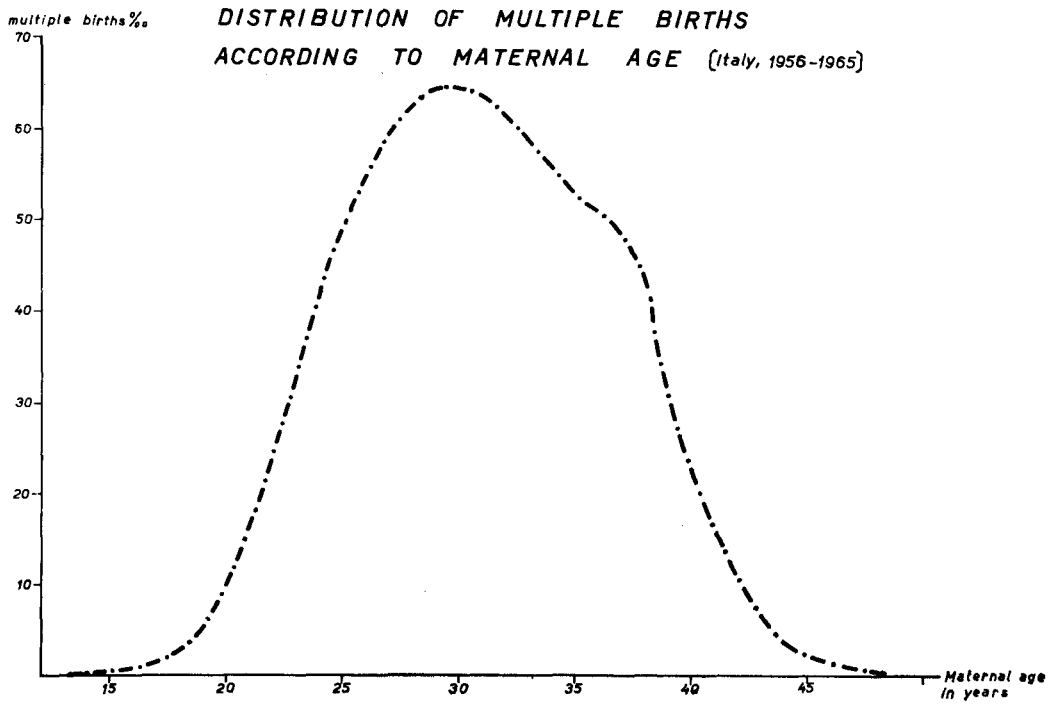


Fig. 2

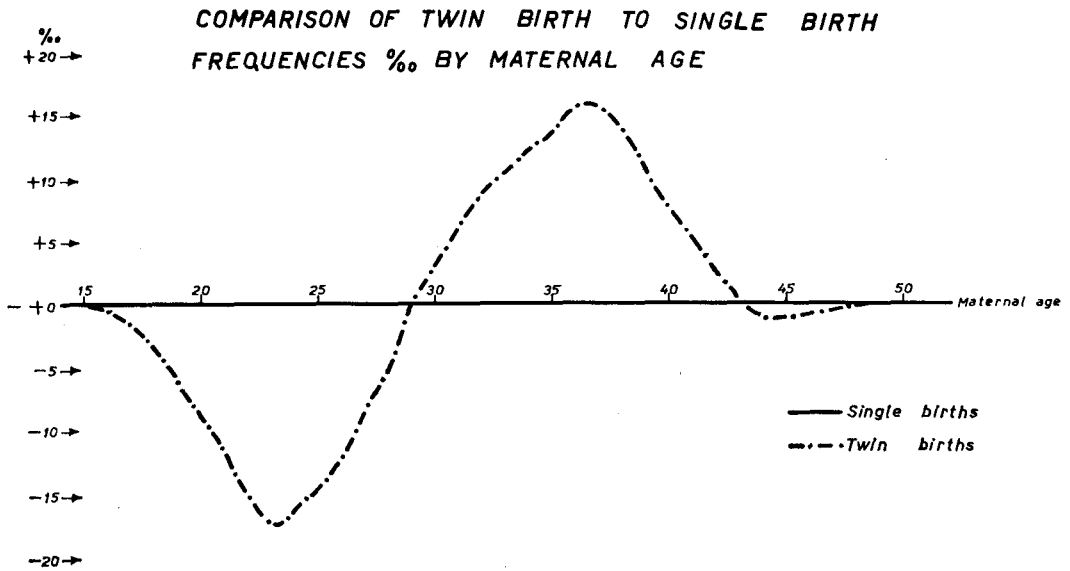


Fig. 3

Considering uniparity as a normal characteristic of the species, we may think that it is due to a regulating mechanism (e.g. to a given increment of FSH which every time produces the unfolding of a single follicle). Such a control is effective when the specific genotype enters into action and begins to be ineffective when this genotype is exhausted.

In this light the behaviour of the curve may be considered. From the 15th to the 23rd year of maternal age, the comparative decrease in twin births seems to reflect the increasing effectiveness of the regulating mechanism for uniparity. On the other hand, from 23 to 39 the opposite seems to occur, i.e. the genotype responsible for the regulating mechanism would undergo a reduction of effectiveness. After 36, the further decrease of effectiveness of the regulating mechanism may produce a further comparative increase, rather than of multiple births, of abnormal births. In fact, in the same period, an increase of miscarriages, stillbirths and malformations may be observed.

Consequently, we may think that the year in which the relatively greater number of mothers become integrated into the control mechanism for uniparity is the 23rd one, whereas the year in which the relatively greater number of mothers loses such a control, due to the exhausting of the specific genotype, is the 36th one.

## Research 2

Our second research aims to compare the differential fertility in mothers of twins and mothers of singletons from the viewpoint of spontaneous abortivity. As a matter of fact one can maintain that spontaneous abortivity is closely correlated to infertility and hypofertility.

For this purpose, we have examined 2000 case histories from the Obstetrical Clinic of Rome University taking into account the number of abortions and the occurrence of twin births.

The occurrence of twin births was used as a criterium for establishing the two fundamental classes of our research; in other words, on one hand, the series of women who gave birth only to singletons (1947); on the other, the series of women who gave birth to at least one twin pair (53).

Of course, the first class may contain some women who until the delivery at the Obstetrical Clinic had not given birth to twins, but may have done so later on.

One may expect such a cause of errors also while studying the frequency of single and twin births in our material and comparing it to the corresponding frequency in the Italian population.

According to ISTAT data the ratio of multiple to single births in the Italian population is about 1 : 85. In our material of 4628 births we have 53 twin births and 4575 single births. Therefore, in our sample the ratio is 1 : 87. On this basis, the error which we may encounter due to the composition of our material, would correspond to 2.30%.

With respect to the number of abortions reported in case histories we may assume it to be reliable because of both clinical interest and professional secrecy, which are in all cases equivalent for both series of mothers.

The results of these studies are recorded in Tables 1 and 2, which show the index of abortivity in mothers of singletons only to be 13.48%, whereas this index goes down to 10.9% for the mothers who have also had multiple births.

These results were controlled by the "t" of Student ( $t = 6.972$ ;  $p < 0.001$ ) which demonstrates the significance of the observed difference.

We are therefore able to express the result of the second research by a diagram

Tab. 1. Sample of mothers of singletons

Dimensions of the sibship	Frequency of sibships according to the number of miscarriages					Total deliveries
	0	1	2	3	4	
1	637	—	—	—	—	637
2	515	121	—	—	—	1272
3	222	94	37	—	—	1059
4	86	52	32	8	—	712
5	15	35	8	7	8	365
6	12	23	6	—	—	246
7	11	3	3	—	—	119
8	1	—	—	1	1	24
9	—	—	—	1	1	18
10	—	1	—	1	1	30
11	—	1	—	1	1	33
12	—	1	—	—	—	12
Total sibships	1499	331	86	19	12	4527
Total miscarriages	—	331	172	57	48	608

$$\text{Index: } \frac{\text{Miscarriages}}{\text{Deliveries}} \times 100 = 13.43$$

(Fig. 4) which shows the different incidence of spontaneous abortivity in mothers of twins and in mothers of singletons.

Spontaneous abortivity is explained by endocrine, neuro-vegetative and metabolic causes and/or by an abnormal morphology of the genital tract and the fetal membranes. Evidently, the incidence of these factors cannot be discriminated in our material. Yet their distribution in our material may be assumed to be random.

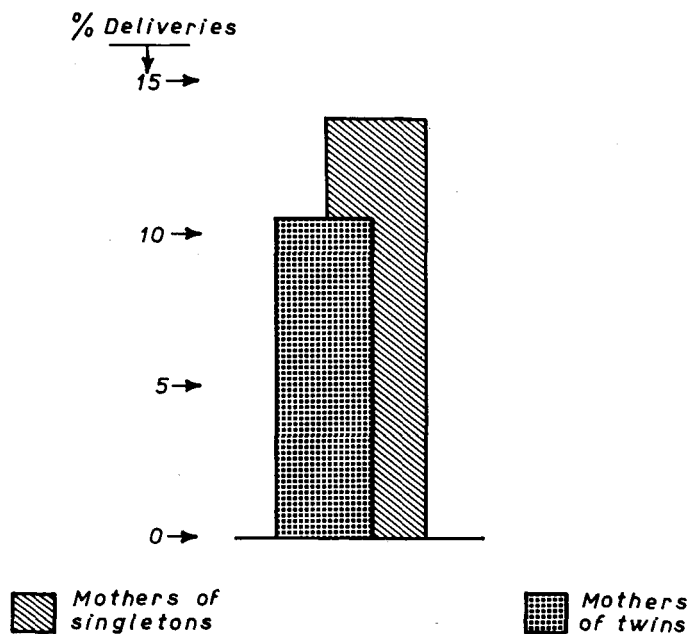
Thus it is possible to state generally that mothers of twins show a spontaneous abortivity lower than that of mothers of singletons and, consequently, from this point of view a higher rate of fertility.

**Tab. 2. Sample of mothers of twins**

Dimensions of the sibship	Frequency of sibships according to the number of miscarriages					Total deliveries
	0	1	2	3	4	
1	10	—	—	—	—	10
2	17	—	—	—	—	34
3	4	4	—	—	—	24
4	4	2	1	1	—	32
5	2	—	—	—	—	10
6	2	—	—	—	—	12
7	1	—	1	—	—	14
8	—	—	—	—	—	—
9	1	—	—	—	1	18
10	1	—	1	—	—	20
11	—	—	—	—	—	—
12	—	—	—	—	—	—
Total sibships	42	6	3	1	1	174
Total miscarriages	—	6	6	3	4	19

$$\text{Index: } \frac{\text{Miscarriages}}{\text{Deliveries}} \times 100 = 10.92$$

**SPONTANEOUS MISCARRIAGES**



**Fig. 4**

### Research 3

Our third research aims to ascertain whether the fertility of a woman in the case of a MZ twin birth is different from the one in the case of a DZ twin birth and, if such a difference exists, which is its expression, its value and its nature.

For this specific research we have put aside the material obtained by vital statistics, a previous study (Gedda and Brenci, 1961) having shown that the diagnosis of zygosity based on population data according to Weinberg's formula is not reliable.

The criterium adopted by Weinberg and based on the number of opposite-sexed (MF) pairs, from which the total number of DZ pairs is calculated (on the assumption of equal sex-ratios for single and twin births) is as follows:  $DZ = 2MF$ ;  $MZ = 1 - DZ$ .

This theory underwent criticism by other authors and by ourselves in 1961. In fact, according to Weinberg's criterium, it is theoretically possible to evaluate the frequency of DZ twin pairs not only from the frequency of MF but also of same-sexed (MM and FF) twin pairs. In so doing, on the basis of Italian twin birth data from 1948 to 1952, we observed that the calculated frequency of DZ twin pairs varies according to the chosen experimental frequency (Tab. 3).

Considering that the diagnosis of zygosity cannot be derived from population

**Tab. 3. Frequencies of monozygosity derived from the following pair frequencies (in %)**

	♂♂	♂♀	♀♀
1948	26.54	29.84	33.15
1949	26.22	30.41	34.59
1950	25.38	29.70	34.03
1951	27.82	29.84	31.86
1952	28.02	29.14	30.20

(ISTAT data)

data by the above method but should be calculated clinically pair by pair by means of the well known serological, anthropological and psychological methods, we turned to the Mendel Institute's "Gemelloteca", gathering a large twin material with a clinically ascertained diagnosis of zygosity. Our study concerned 1607 pairs (552 MZ and 1055 DZ).

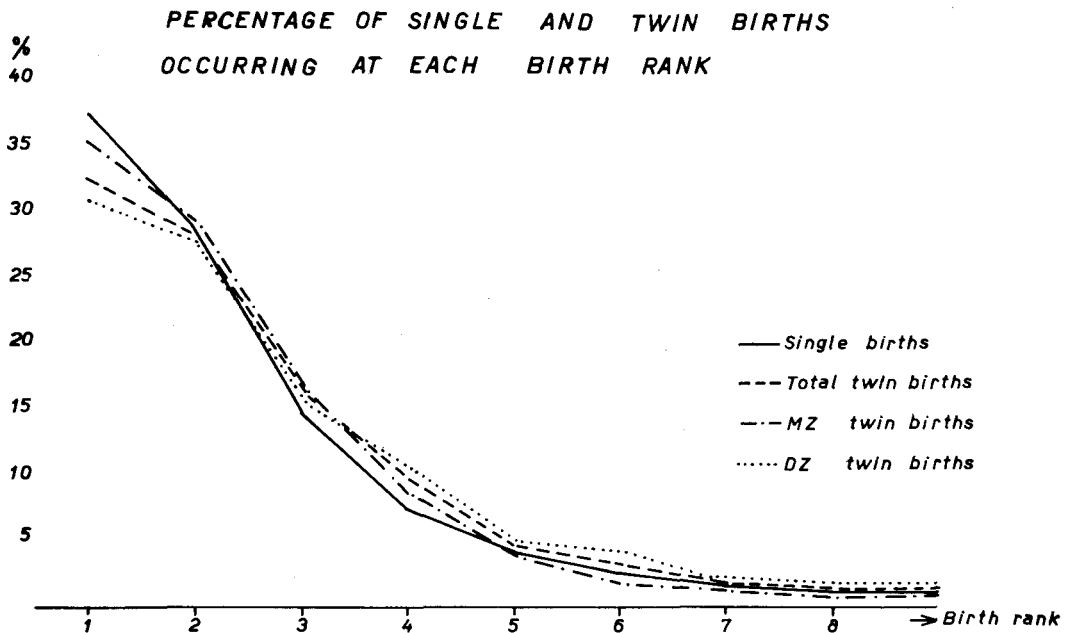
As a criterium to compare fertility respectively in mothers of MZ pairs and of DZ pairs, we chose birth rank. We did not choose the age at the delivery of twins, because this could not be surely reconstructed in all the cases we studied, while, on the other hand, birth rank and maternal age are highly correlated.

The twin pairs we studied were born between 1955 and 1968. For this given pe-

riod birth frequencies by birth rank were drawn from population data, and the same calculation was applied to determine twin birth frequencies in general from the same data. On the other hand, we used the data from our "Gemelloteca" to calculate the frequency of MZ and DZ twin births according to birth rank. These four series of percentage values are shown in Tab. 4 and Fig. 5. These data clearly show a sig-

**Tab. 4. Percentage of single and twin births occurring at each birth rank**

Birth rank	1	2	3	4	5	6	7	8	8 and above
Single births	37.8	29.4	14.4	7.6	4.2	2.5	1.5	1.0	1.6
Total twin births	32.9	28.5	16.7	10.1	4.8	3.4	1.5	1.0	1.1
MZ twin births	35.5	29.5	16.8	8.9	4.2	2.0	1.3	0.9	0.9
DZ twin births	31.5	28.0	16.7	10.7	5.2	4.1	1.6	1.1	1.1





nificant difference between total frequencies of twin and single births by birth rank (cf also Fig. 6).

This is all the more evident when we compare the curves of MZ and DZ twin births by birth rank, equalized to single births of the same rank. In this way two characteristic developments may be shown, corresponding to the two different types of twin births. MZ twin births show a higher frequency than DZ ones in the first birth rank, although both are lower than the line for single birth frequency.

At the second birth rank, the MZ frequency is above the line for single births,

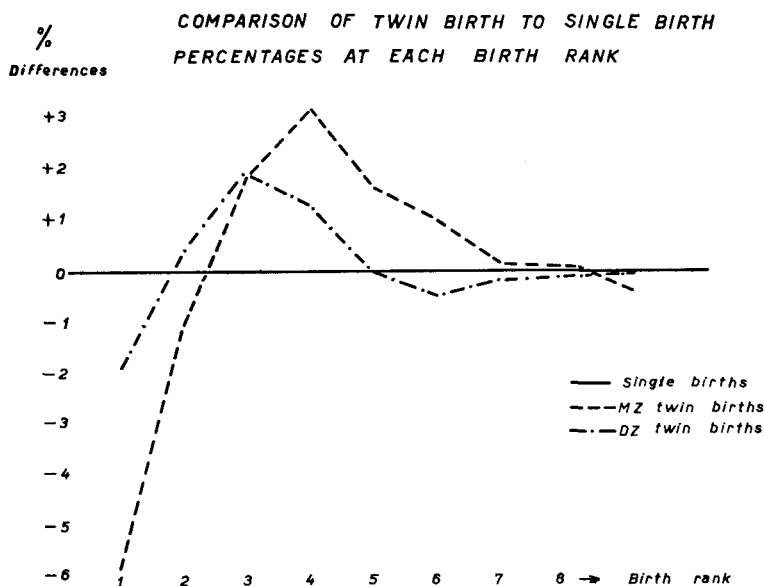


Fig. 6

while the DZ frequency is still below. MZ's and DZ's reach the highest frequency respectively at the third and the fourth birth rank. At the fifth rank for MZ's and the seventh for DZ's the respective frequencies cease to differ significantly from the single-birth line.

These results show that, during the period of relative increase of twin births (referred to in the first research) MZ's and DZ's play a different role, indicating an anticipation and a narrower range of the increase of MZ's with respect to DZ's.

Since our evaluation was based on the fact that maternal age and birth rank are highly correlated, our results on MZ births differ from those obtained by Yerushamly and Sheerer (1940), who considered the frequency of MZt win births to be practically independent from maternal age.

## Discussion and Conclusions

Summarizing the results of our researches we have observed:

- a) A differential behaviour of the ratio uniparity/multiparity with respect to maternal age;
- b) A differential incidence of miscarriages in uniparity and multiparity;
- c) A differential behaviour of MZ and DZ twinning with respect to birth rank.

A unifying interpretation of the above results seems to lead to the following observations:

- a) Multiparity may represent a genetically reduced effectiveness of the regulating mechanism responsible for uniparity in the human species. A woman may thus revert to phylogenetic multiparity.
- b) The resulting multiparity seems to be a function of the chronological parameter of the normal genotype (Gedda, 1961); the latter, defined as "chronon" (Gedda, 1965) would in such cases be shortened.
- c) Multiparity seems to reflect from more than one point of view a condition of increased fertility.
- d) Monozygosity and dizygosity are two separate phenomena within multiparity; yet their behaviour with respect to single births and maternal age is similar.

## Summary

The study of Italian Vital Statistics, from 1957 to 1966, reveals various classes of fertility (sterility, infertility, mean fertility, hyperfertility) and the curve of fertility in the woman's biological time. The study of lying-in women in Obstetrics Departments also yields data revealing an interaction between class and moment of fertility. The study of the Mendel Institute's twin file finally yields data stressing the existence of a relation between hyperfertility and multiple births. Endocrine fertility may thus be considered as genetically conditioned, and multiple births as an epiphenomenon of the hyperfertile class.

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#### RIASSUNTO

Lo studio delle statistiche demografiche italiane dal 1957 al 1966 rivela varie classi di fertilità (sterilità, infertilità, fertilità media, iperfertilità) e la curva della fertilità nel tempo biologico della donna. Lo studio delle degenti nei reparti delle Cliniche Ostetriche fornisce anche dati che rivelano una interazione fra classe e momento di fertilità. Lo studio della casistica gemellare dell'Istituto Mendel fornisce infine dati che sottolineano l'esistenza di una relazione fra iperfertilità e nascite multiple. La fertilità endocrina può quindi essere considerata come geneticamente condizionata, e le nascite multiple come un epifenomeno della classe iperfertile.

#### RÉSUMÉ

L'étude des statistiques démographiques italiennes de 1957 à 1966 indique différentes classes de fertilité (stérilité, infertilité, fertilité moyenne, hyperfertilité) et la courbe de fertilité dans le temps biologique de la femme. L'étude des femmes observées dans les Cliniques Obstétricales fournit aussi des données qui révèlent l'existence d'une interaction entre classe et moment de fertilité. L'étude des archives gémellaires de l'Institut Mendel fournit enfin des données qui soulignent l'existence d'une relation entre hyperfertilité et naissances multiples. La fertilité endocrine peut donc être considérée comme génétiquement conditionnée et les naissances multiples comme un épiphénomène de la classe hyperfertile.

#### ZUSAMMENFASSUNG

Das Studium der italienischen Bevölkerungsstatistiken in den Jahren 1957-1966 ergibt verschiedene Fertilitätsklassen (Sterilität, Unfruchtbarkeit, durchschnittliche Fertilität, Hyperfertilität) sowie eine Fertilitätskurve in der biologischen Zeitspanne der Frau. Bei Forschung über Frauen, die in den Geburtskliniken, liegen, zeigt sich auch aus den Erhebungen eine Wechselbeziehung zwischen Fertilitätsklasse und Fertilitätsmoment. Die Untersuchung der Zwillingskasuistik des Mendel-Instituts weist schliesslich noch darauf hin, dass ein Zusammenhang zwischen Hyperfertilität und Mehrlingsgeburten besteht. Man kann somit die endokrine Fertilität als erbbedingt und die Mehrlingsgeburten als Epiphänomen der Hyperfertilitätsklasse betrachten.