

# The theoretical formulae of maternal and child health indicators of twin births per mother

Syuichi Ooki\*

Department of Health Science, Ishikawa Prefectural Nursing University, Ishikawa, Japan

## Abstract

**Background:** The maternal and child health indicator at birth has thus far been calculated per child irrespective of plurality, where both the numerator and denominator are the number of children. However, this calculation method is not necessarily appropriate when dealing with the frequency of mothers who give birth to affected children, since mothers of multiples give birth to more than one baby at once.

**Methods:** The theoretical formula of frequency of disease at birth and relative risk of twin pregnancy with singleton pregnancy as reference group can be derived mathematically.

**Results:** In mothers of twins, the likelihood of giving birth to at least one affected child depends on the pairwise concordance rate of the twin pairs. The relationship between relative risk of disease at birth per child (twins/singletons:  $RR_1$ ) and per mother (mothers of twins/mothers of singletons:  $RR_2$ ) are theoretically derived as formulas using a pairwise concordance rate ( $x$ ). The derived formula was  $RR_2 = 2/(1+x) \times RR_1$ , showing  $RR_2$  approaches two times  $RR_1$  as the concordance rate decreases.

**Conclusion:** When counseling a family for twin pregnancy, it is important to inform them that the risk of having at least one affected child in one family could actually increase in multiple pregnancy on a purely statistical basis, due to the increased potential for discordant pairs.

## Introduction

The maternal and child health indicator at birth has thus far been calculated per child irrespective of plurality, where both the numerator and denominator are the number of children. Even when the frequency was calculated per pregnancy, namely the denominator is the number of mothers or pregnancies, the numerator is typically the number of affected children, not the number of mothers who give birth to an affected child. This calculation of disease frequency is not necessarily appropriate for mothers of multiples who give birth to more than one child at once. The expectant mother of twins wants to know the likelihood of having two healthy children, not “at least one healthy child”.

This simple fact has never been highlighted. The purpose of the present study is to examine a theoretical model of maternal and child health indicators at birth per mother and apply them to birth data to clarify the epidemiological characteristics of relative risk per mother experiencing multiple pregnancy.

## Methods

To clarify, the simplest case of twin pregnancy is treated below. The theoretical formula of frequency of disease at birth and relative risk of twin pregnancy with singleton pregnancy as reference group can be derived mathematically. This formula was applied to available data, including (1) vital statistics of stillbirth and (2) birth defects data after assisted reproductive technology (ART) in Japan. The author used the prevalence (proportion), instead of the incidence, throughout the calculations. If the two twins differ as to whether they have diseases at birth, they are discordant; if they both have diseases at birth, they are concordant.

## One simple example of the difference between disease frequencies calculated per child and per mother

Supposing that ten singletons are born from ten mothers, and ten twins (five twin pairs) are born from five mothers. Of them, two children had certain birth defects during pregnancy or at birth in both groups. In this case the frequency of affected children is 0.2 (=2/10) for both singletons and twins. This frequency is calculated per child, where both numerator and denominator are the number of children. Thus, the relative risk of twins with singletons as a reference group ( $RR_1$ ) is 1.0 (=0.2/0.2) per child.

When calculating the frequency of disease per mother, both the numerator and denominator should be the number of mothers. The frequency of mothers with at least one affected child in one pregnancy/delivery is not necessarily equal in the two groups. In the case of singletons, the frequency of mothers with an affected child is 0.2 (two mothers out of ten mothers) and is equal to that calculated per child (two children out of ten children). However, in the case of twins this is not necessarily correct. If two affected twins are born from one mother, i.e., a concordant pair, the frequency of mother with affected children

\***Correspondence to:** Syuichi Ooki, Department of Health Science, Ishikawa Prefectural Nursing University, 1-1, Gakuendai, Kahoku, Ishikawa, 929-1210, Japan, TEL & FAX: +81-76-281-8377; E-mail: sooki@ishikawa-nu.ac.jp

**Key words:** mothers of twins, pairwise concordance rate, stillbirths, birth defects, maternal and child health indicators at birth

**Received:** December 05, 2018; **Accepted:** December 17, 2018; **Published:** December 24, 2018

is 0.2 (one mother out of 5 mothers). In this case, the relative risk of mothers of twins with mothers of singletons as the reference group ( $RR_2$ ); the relative risk per mother is 1.0 ( $=0.2/0.2$ ). On the other hand, if the two affected twins are born from different mothers, i.e., from two discordant twin pairs, the frequency of mothers with affected child is 0.4 (2 mothers out of 5 mothers). In this case,  $RR_2$  is 2.0 ( $=0.4/0.2$ ). Clearly, it is important to take into account the percentage of disease-concordant and discordant twin pairs in calculating  $RR_2$ .

**Two applications of birth data to the formula**

Given this basic idea, the author derived a general formula showing the relationship between  $RR_1$  and  $RR_2$  and applied it to vital statistics of stillbirth and data from birth-defect studies.

**1. Vital statistics of stillbirth:** The reason why stillbirth data were selected is as follows. Japanese vital statistics offer almost complete data regarding stillbirths in twin pairs. Moreover, stillbirth data are the only data presented as pairwise data for twins in vital statistics. Using vital statistics of stillbirths from 1995 to 2017 (all available data), the frequencies of stillbirth of singletons and twins, and frequency of mothers with stillbirth delivery could be calculated with excellent accuracy, and the concordance rate of twins, and  $RR_1$  and  $RR_2$  could also be calculated, to show the epidemiological characteristics of stillbirths.

**2. Birth defects after ART:** The method for collecting ART data has been described elsewhere [1]. Almost all medical institutions performing ART are registered with the Japan Society of Obstetrics and Gynecology (JSOG). From 2004 on, the list of all ART pregnancies resulting in birth defects is presented every year in the JSOG annual reports on ART (in Japanese). The author used these case report data from 2004 to 2012 as initial information on birth defects. The types of birth defects were reclassified according to the International Classification of Diseases, tenth edition (i.e., ICD-10, 2003 version). Diseases that were classified in the categories of ICD-10 code Q00-Q99 (i.e., congenital malformations, deformations and chromosomal abnormalities) were selected and analyzed in the present study. The present author paired twins using information on birth year, maternal age, gestational weeks, method of ART, blastocyst implantation, and plurality.

Moreover, previous national studies dealing with the concordance rate of twins of any birth defect, rather than specific birth defects, were selected and reanalyzed, since families with pregnant women might be more interested in the overall risk of birth defects. This means that a pair is concordant if they both have “any kind of birth defect”; i.e., if one has one birth defect and another has a different birth defect.

**Results**

**Theoretical formula of relative risk per mother**

If the number of affected children is p out of M in total singleton births and q out of N in total twin births, the frequency of affected children is p/M in singletons and q/N in twins, respectively. Thus,  $RR_1$  is equal to  $(q/N) / (p/M)$  by definition.

The frequency of having an affected child per mother, where the frequency of mother with at least one affected child in one pregnancy, is the same as the frequency of affected children per singleton-born children, since the number of children in one pregnancy is one. So, the frequency of mothers with affected children among singletons remains p/M, which is equal to the frequency of affected singletons. However, the frequency of twin-bearing mothers with affected children is not the

same as the frequency of affected twins calculated per child, since the number of children in one twin pregnancy is two. If the number of total twin children is N, the total number of mothers with twins is N/2. If the number of mothers who give birth to ‘at least one affected child (twin),’ namely ‘one affected and one non-affected’ or ‘two affected’ is r, the frequency is  $r/(N/2)$  or  $2r/N$ . Thus,  $RR_2$  is equal to  $(2r/N) / (p/M)$ . The relationship between  $RR_1$  and  $RR_2$  is thus defined as the formula:

$$RR_2 = (2r/q) \times RR_1 \tag{1}$$

The pairwise concordance rate is the probability that both members of a twin pair are affected if at least one member of the pair is affected [2]. The pairwise concordance rate (x) was calculated as  $C/(C+D)$ , where C denotes the number of affected concordant pairs and D denotes the number of discordant pairs. In the setting of present study,  $q=2C+D$  represents the number of affected twins and  $r=C+D$  represents the number of mothers with at least one affected twin, respectively. Using C and D, the frequency of mothers with at least one affected twin is defined as  $2r/N=2(C+D)/N$ .

Using C and D, we get the formula:  $x=C/(C+D)$

and  $r/q= (C+D)/(2C+D)$

To calculate the invers of x, we get the formula:

$$1/x=1+D/C \tag{2}$$

To divide both the denominator and numerator of  $(C+D)/(2C+D)$  by C, we can get the formula:

$$r/q= (C+D)/(2C+D) = (1+D/C)/(2+D/C) \tag{3}$$

Using the formulae (1), (2) and (3), we lead to the following simple formula:

$$RR_2 = (2r/q) \times RR_1 = 2(r/q) \times RR_1 = 2(1+D/C)/(2+D/C) \times RR_1 = 2(1/x)/(1+1/x) \times RR_1 = 2/(1+x) \times RR_1 \quad (0 \leq x \leq 1)$$

This final formula  $RR_2= 2/(1+x) \times RR_1$  shows that  $RR_2$  is in inverse proportion of the concordance rate.

**Application of formula to the data of stillbirths and birth defects**

**Stillbirths:** The results are shown in Figures 1 and 2. The frequency of stillbirths of twins both per child and per mother has tended to decrease over past 20 years, as shown in Figure 1.  $RR_1$  and  $RR_2$ , however, have not necessarily decreased. In fact,  $RR_2$  has increased in recent years, as shown in Figure 2. Pairwise concordance rates have been constant at around between 0.6 and 0.7, and thus  $RR_2$  was 1.2 times that of  $RR_1$  ( $RR_2=1.2 \times RR_1$ ).

**Birth defects:** Regarding birth defects after ART from 2004 to 2012, 2,788 singletons out of 294,629 singleton pregnancies and 393 twins (358 mothers) out of 46,062 twins (23,031 twin pregnancies) had birth defects. Of 393 twins out of 358 mothers, 35 pairs were concordant, and 323 pairs were discordant. Thus, the pairwise concordance rate for birth defects was calculated to be 0.098 and  $RR_2$  was equal to  $1.82 \times RR_1$ . In this case,  $RR_1$  and  $RR_2$  could also be calculated directly ( $RR_1=0.90$ , with 95% confidence interval [0.812, 1.002] and  $RR_2=1.64$  with 95% confidence interval [1.473, 1.832]).

The results of previous studies of birth defects are shown in Table 1. Four national studies [3-6] that calculated the concordance rate of “any birth defect” were found and yielded a total concordance rate

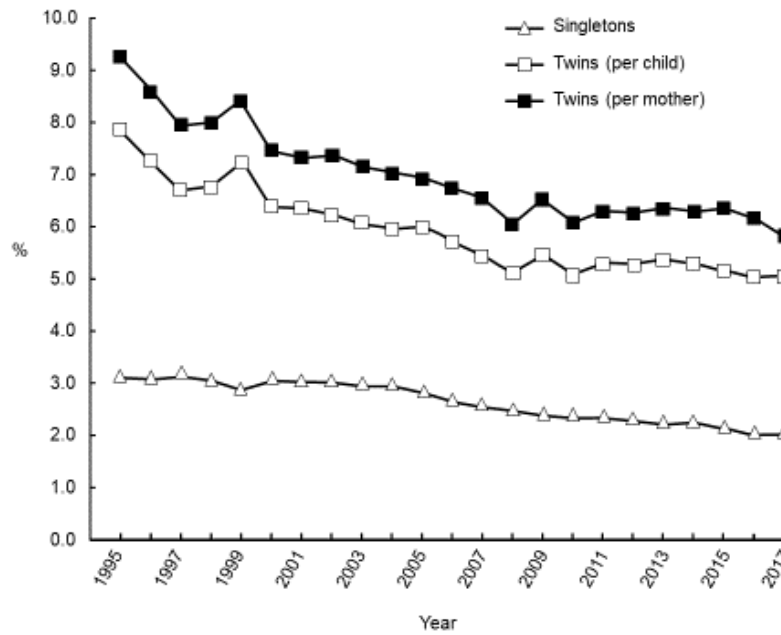


Figure 1. The frequencies of stillbirths of twins and singletons per child and per mother (Japanese vital statistics from 1995 to 2017)

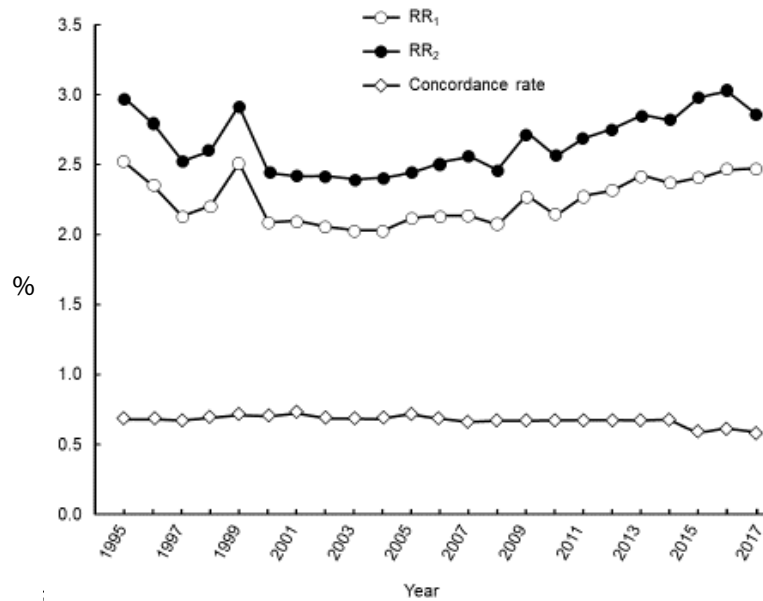


Figure 2. Relative risk of stillbirths of twins with singletons as references group per child ( $RR_1$ ) and per mother ( $RR_2$ ), with concordance rate ( $x$ ) of twin pairs ( $0 \leq x \leq 1$ )

Table 1. Concordance rates of birth defects in the literature of twin studies

Author(s)	Year of data collection	N of pairs	Data source	Twin pairs		Pairwise concordance rate
				Concordant (N pairs)	Disconcordant (N pairs)	
Myriantopoulos [1976]	Not mentioned	615	Collaborative perinatal project	29	125	0.188
Imaizumi et al. [1990]	1974	12,392	Population-based	22	34	0.393
Kato & Fujiki [1992]	1979-1990	968	Hospital-based	3	39	0.071
Campana & Roubicek [1996]	1982-1995	690	Hospital-based	5	25	0.167
Total				59	223	0.209

of 0.209 (59 concordant pairs and 223 discordant pairs), making  $RR_2 = 1.65 \times RR_1$  (The sample size of each study was not taken into account in the calculation).

## Discussion

### The importance of maternal and child health indicators per mother

When calculating the likelihood of a pregnant mother to have at least one affected baby at birth, the number of children per pregnancy, i.e. plurality, must be considered. For example, when supporting families with twin children, including counseling of couples who hope to undertake fertility treatment, especially ART, it is important to inform them of the probability of having two healthy babies, and conversely, the probability of having “at least one affected child at one pregnancy.” The frequency or relative risk of disease at birth per mother is essentially equal to those indicators calculated per pregnancy/delivery or per family, because the number of mothers, pregnancies/deliveries and families is equal in general.

Concordance or discordance of disease in twins is seldom considered as a birth indicator in studies dealing with multiple births. There exist very few studies that offer both the frequency of disease or health condition according to plurality (singletons vs. twins) and the data of twins as a pair (concordant vs. discordant). Therefore, it is very difficult directly to compare the disease frequency between singletons and twins per child and per mothers at the same time.

### The explanation of theoretical formula of relative risk per mother

The present formula  $RR_2 = 2/(1+x) \times RR_1$  shows that if the concordance rate (x) increases, namely if the concordance rate approaches 1,  $RR_2$  approaches  $RR_1$ . On the other hand, if the concordance rate decreases, namely the concordance rate approaches 0,  $RR_2$  will approach two times the  $RR_1$ . Therefore, if the frequency of discordant twin pairs regarding diseases or health condition at birth, the frequency of mothers with at least one affected twin will also increase.

In addition, this simple formula demonstrates that even if the disease prevalence is equal between singletons and twins, i.e.  $RR_1 = 1$ ,  $RR_2$  is always larger than 1, since the concordance rate is always under 1.

### The effect of ART for families with twins

Spontaneous twin pairs contain both monozygotic (MZ) and dizygotic (DZ) twins, whereas most twin pairs after ART are DZ pairs. In general, the concordance rate of birth defects is higher in MZ pairs compared to DZ pairs, because of the genetic contribution of birth defects. Therefore, it is expected that the concordance rate of birth defects is higher in spontaneous twinning, which contains MZ pairs, compared to ART twins, comprising mainly DZ pairs. This suggests that ART increases the  $RR_2$  of mothers/families with at least one affected twin during pregnancy or at birth by increasing the number of discordant DZ pairs compared to the case in spontaneous twinning. However, caution is needed because DZ twins are in general healthier than MZ twins.

### The characteristics of RR

It is important that RR is not necessarily a direct indicator of frequencies of diseases. In the case of stillbirths, the concordance rate

is relatively high, yielding an  $RR_2$  value that is close to that of  $RR_1$ . But, even if the frequency of stillbirths per child decrease, the frequency of stillbirths per mother do not necessarily decrease, because discordant pair (one stillbirth and one live birth) might increase.

The concordance rate of birth defects, however, is relatively low, yielding a  $RR_2$  value that is close to that of two times  $RR_1$ . This means that families with twins having at least one birth defect are more prevalent than medical specialists believe, since most medical specialists consider only the frequency of birth defects per child, not per mother.

### Relative risk per family of higher order multiples or disease after birth

In the case of higher-order multiples, the percentage of birth defects would be still higher compared to that in twins, while the likelihood of all babies in a pregnancy (for example, in the case of triplets, all three babies) having a birth defect would be lower, meaning that families with at least one affected child would extremely increase on a strictly statistical basis, irrespective of any biological risk incurred by the gestation conditions of multiple births.

The present idea might also be applicable to disease or health problems after birth. However, caution is needed given that when two singleton siblings are in one family, they have the same disease or health problem. In this case, the concordance rate of sibling pairs should be considered.

According to Japan's vital statistics, the total fertility rate has tended to decrease and has fallen well below two (it was 1.43 in 2017) over a long period of time. This suggests that the risk of having at least one affected baby in one family may become higher in families with multiples, which by definition have at least two children, than in families with singletons, which have fewer than two children on average.

## Conclusion

If a couple becomes pregnant with twins, they hope to give birth to two healthy babies, not “at least one healthy baby.” Therefore, when supporting families with multiple pregnancy, including counseling for fertility treatment, it is important to inform them correctly that the possibility of having “at least one affected child” in one pregnancy or in one family statistically increases after twin pregnancy. This simple fact seems not adequately recognized by medical specialists or support workers for families with multiples.

## Acknowledgements

I would like to thank Toshimi Ooma for assistance with the data analysis. This work was supported by JSPS KAKENHI Grant Number JP15H04785.

## Disclosure

The authors declare no conflicts of interest in this work.

## References

- Ooki S (2013) Concordance rates of birth defects after assisted reproductive technology among 17,258 Japanese twin pregnancies: A nationwide survey, 2004-2009. *J Epidemiol* 23: 63-69.
- McGue M (1992) When assessing twin concordance, use the probandwise not the pairwise rate. *Schizophr Bull* 18: 171-176. [[Crossref](#)]

3. Myriantopoulos NC (1976) Congenital malformations in twins. *Acta Genet Med Gemellol (Roma)* 25: 331-335.
4. Imaizumi Y, Asaka A, Inouye E (1990) Fetal deaths with birth defects among Japanese multiples, 1974. *Acta Genet Med Gemellol (Roma)* 39: 345-350.
5. Kato K, Fujiki K (1992) Multiple births and congenital anomalies in Tokyo Metropolitan Hospitals, 1979-1990. *Acta Genet Med Gemellol (Roma)* 41: 253-259.
6. Campana MA, Roubicek MM (1996) Maternal and neonatal variables in twins: an epidemiological approach. *Acta Genet Med Gemellol (Roma)* 45: 461-469. [[Crossref](#)]