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Incidence of abnormal outcome of maternal rubella

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Introduction

The association of maternal rubella and congenital defects is generally accepted in the medical professions today. However, this recognition that viral infections in expectant mothers could cause defects in the products of conception was brought to the attention of the medical profession by Gregg in 1941. Gregg, an Austrailian ophthalmologist, described in a retrospective study a high incidence of congenital cataracts in children whose mothers (87%) could recall having a disease with characteristics similar to those of rubella in the early part of their pregnancies.

Since that time numerous articles have appeared in journals relating maternal rubella and congenital defects, thus creating increased interest among physicians and laymen alike.

It is with this interest in mind that this paper is undertaken in hope that some correlation of such wide variations of statistics and opinions can be made.

Rubella

Rubella is a benign contagious disease of viral etiology, characterized by fever, lymphadenopathy, and morbilliform rash.

The incubation period of rubella is usually about 18 days but may vary from 10 to 25 days. A distinct prodromal period may or may not antedate the rash but, if present characteristically, a mild fever and vomiting may be noticed. Unlike measles, the respiratory manifestations are minimal. The most characteristic sign, postauricular and cervical lymphadenopathy, begins about 6 days before the rash and reaches its peak at the height of the rash.

An exanthem at the junction of the hard and soft palates may be present but with less consistancy than the Koplik spots in measles. The rash first appears on the neck and face as small pink macules, which darken and spread downward over the trunk and extremities within 24 hours. The palms and soles are usually not involved. The rash rarely persists beyond the fourth day. There is no specific treatment, and the vast majority of cases recover uneventfully.

In the differential diagnosis of rubella one must consider the possibility of mild rubella, scarlet fever, and exanthem subitum. Also, early in the differentiation, infectious mononucleosis may be difficult to rule out because of the similarity in rash and lymph node

involvement. As with any body rash, drug eruptions may be considered.

Maternal Rubella

Maternal rubella constitutes any pregancy in which rubella has been contracted by the female bearing the products of conception. No limitations are placed on this in referrence to time or the sequence of events. However, it is universally accepted that the critical time for such, in referrence to the fetus, is during the firs trimester of pregnancy. It is in this period when organogenesis occurs.

The critical times in organogenesis are not known precisely but in general are as follows: heart, 4-9 weeks; lens, 5-8 weeks; and cochlea 7-12 weeks. From this, one may assume then that any stress placed on these tissues at the said critical times might result in defects of that tissue.

The teratogenic factors considered to play an important role in the development of the fetus may be divided into two large groups; I-hereditary or genetic, and II-maternal. The maternal factors suggested are infections such as rubella, syphilis, and toxoplasmosis; irradiation; vitamin deficiencies, and anoxia.

If the above teratogenic factors were to occur at the critical periods of organogenesis and would be of sufficient magnitude in stress on these organs, then one may reason that abnormalities

might be produced in said organs.

In the cse of rubella, the virus gains entrance to the circulation of the maternal blood and passes the placental barrier to the fetal circulation and thence to the tissues of the new developing organs. The virus enters the cells, causing destruction of the cytoplasm of the involved cells. Depending upon the stage of organogenesis, the defect may or may not be of significance.

The serious anomalies such as congenital heart defects and cataracts probably develop during the first eight or nine weeks while those involving the ear may develop later up to about twelve weeks gestation. With this same idea in mind, there would be few defects developing after about this time in gestation. Ashe and Arey have in fact suggested that cataracts develop during the 27-35 day, cardiopathies during 36-49 days, and deafness 50-63 days.

A woman who contracts German Measles during pregnancy usually confronts her local doctor with a number of difficult and disconcerning questions:

1. What are the possibilities that her child will be affected?
2. What defects may be anticipated?
3. Are the defects or deficiencies permanent or can they be restored to a normal functional level?
4. Is it proper to perform an abortion in order to prevent birth of a

defective child?

5. Should gamma globin be used? Is it beneficial in German Measles and will it prevent anomalies in the child?

Types of Congenital Defects

The types of congenital defects are numerous and variable. They range from those that are so mild in nature as to be completely compatible with life to those so severe as to cause abortions or stillbirths. Also these congenital defects may manifest themselves singularly or in combination with others.

The defects associated with maternal rubella have been grouped into what is known as the "Rubella Syndrome." This syndrome has come from data supplied by retrospective studies in which the workers established the types of anomalies most likely to result when the mother had rubella in the first trimester of pregnancy.

This group of defects consists of congenital cataracts, congenital heart disease (patent ductus arteriosus and ventricular septal defect), congenital deafness, microcephaly, mental deficiency and dental deformities. Some workers suggest that microphthalmus should also be included.

These defects are not limited to maternal rubella for they have been observed in association with other teratogenic factors such as other viral infections and irradiation.

Incidence of Congenital Abnormalities When Rubella Intervenes

The incidence or rate of congenital abnormalities following maternal rubella has been said to vary between 0.0 and 100.0%. Such a broad statement is completely meaningless and misleading and therefore should be avoided. The interpretation of such wide variations of statistics is impossible, and confusing to physicians and patients alike.

In referring to incidence of any condition, one must apply certain limits to the situation. So it is also with congenital abnormalities following maternal rubella. For instance, the term congenital abnormality simply means a condition contrary to the usual existing at, and usually before, birth. In this definition there is no limit placed on the type of, severity of, or the complications of the situation that differs only from the usual at birth.

Follow-up studies are extremely important in arriving at the incidence of congenital abnormalities. Lock, in a study of 176 children for congenital anomalies, found that certain ones cannot be found on first examination, but become evident later.

On the first examination, Lock found 32 definite and 27 questionable abnormalities in 35 of 176 children. However, on the second examination done at 16 to 25 months of age, only 7 of the

questionable anomalies proved to be significant while 12 previously unsuspected serious abnormalities were found.

Similarly, McIntosh reported an overall incidence of 7.0% malformations in 5,964 births. Among these malformations only 43.2% were recognizable at birth. He also reported that 18.1% were not detected until the child was one year of age or more.

Another limiting factor in arriving at the incidence of congenital anomalies following maternal rubella is in reference to the type of study reported; that is, whether retrospective or prospective studies were done. For example, Collins reported a retrospective study of 383 cases of maternal rubella with 70 to 80% congenital anomalies while Blattner in a prospective study reported only a 10 to 12% incidence. The difference between the two is reflected in the fact that retrospective studies are not done on random samples from a common universe.

Some other factors also influencing the incidence of congenital anomalies following maternal rubella have been suggested. A very important one is that there is no possible way of knowing whether a congenitally malformed infant would have been so if the mother had not contracted rubella. Another, suggested by Krugman, is that clinically-recognized rubella may not always be present since these abnormalities may occur following subclinical infection. Pitt also

suggests that no evidence exists indicating the severity of rubella differs between mothers of affected infants and mothers of normal infants. It is also conceivable that many mothers have rubella during pregnancy and do not recognize it as such and also that a few cases have escaped the attention of physicians in their diagnosis and/or reports.

With results of studies and interpretations like any of the above, one should view with caution any data on frequency of congenital defects from maternal rubella or any other cause.

Incidence by Trimesters

The normal 280 days of gestation in human pregnancies have been divided arbitrarly in obstetrics into three equal periods known as trimesters. Each trimester thus contains about 13 weeks. Of the three divisions of gestation, the first trimester is of greatest importance in referrence to congenital defects since it is in this trimester that the teratogenic factors determine the characteristics of the fetus.

Rubella has been before stated to be one of the maternal teratogenic factors and thus it seems natural that its effect in producing congenital defects would be most influential during the first trimester.

Kantor and Strother reported a total of 92 patients who contracted rubella during pregnancy. Of these 72 were in their first trimester and 20 were in the second and third. The 72 cases with maternal rubella were further subdivided into 55 term deliveries and 17 abortions. Of the 55 term deliveries 85% were normal, 11% were born with defects and 4% were still born. The 20 cases in the other trimesters were all normal.

From the above one can see that in 92 cases of maternal rubella irregardless of trimester, about 72% of the cases were normal.

However, if the results of the studies are limited to trimesters the percentage of normal infants of the second and third trimester cases is 100% and that of the first trimester is decreased to about 65%.

With results like this, one can readily see why the prognosis of maternal rubella depends a great deal on the time in gestation. Even limiting the time to trimesters is insuffecient; therefore, a few workers have reported results in terms of eight weeks (Mullins) and others have gone further to report in incidences for each four weeks. Incidences such as this will be discussed later.

A review of several articles was made and the incidence of abnormal outcome of maternal rubella reported by these authors was compounded from their results. It was found that the incidence of such was about 31% when maternal rubella was contracted in the first trimester and about 3.4% when contracted during the last two trimesters. (See table I)

Ashe and Arey report a similar review of reports given by five authors. However, in this review prematurity was also included. Since this is included, one would expect the average of abnormal outcomes to be even higher but this was not the case, (see Table II). The difference in the percentages of abnormal outcome cannot be readily explained since both series include a considerable number

of cases. The main agreement of the two series is the incidence of abnormal outcome is greater in the first trimester than in the second two trimesters.

Table I

Incidence of abnormal outcome of maternal rubella.

Inclusive of: spontaneous abortion
still born
congenital defect
neonatal deaths
Exclusive of: therapeutic abortions
prematurity

Trimester		total # of cases reported	#normal births	% of abnormal
1-13 weeks	Lock	29	15	41%
	Greenberg	46	28	39%
	Kantor	72	47	35%
	Manson	202	151	25%
	Mullins	11	3	72%
	Pitt	145	114	21%
	Siegel	104	62	60%
	TOTAL	609	420	31.3%
14-40 weeks	Lock	46	44	4.3%
	Kantor	20	20	0.0%
	Mullins	11	11	0.0%
	Siegel	190	183	3.7%
	TOTAL	267	258	3.4%

Table II

Incidence of abnormal outcome of maternal rubella.

Inclusive of: prematurity
still born
congenital anomaly
neonatal deaths
Exclusive of; therapeutic abortions

Trimester			
1-13 weeks	Ashe (review of 5 authors)	817	19%
14-40 weeks	Ashe (review of 5 authors)	555	10%

Incidence by Weeks

It would truly be a contribution to society if a physician could predict fetal anomalies and congenital defects in an infant seven or eight months before he was even born. In a way this is what the medical field is trying to do in referrence to maternal rubella as a cause of congenital defects. It began with retrospective studies in 1941, on to prospective studies in the early 1950's, and then on to be reported as incidences according to trimesters. However, as stated earlier, some authors have carried the studies further and are now reporting incidences of abnormal outcomes calculated on the basis of weeks rather than trimesters.

Ideally the situation would be one where a physician, knowing the week of gestation at which the onset of symptoms of a viral disease occured, could give an accurate estimate of the risks to the fetus. With such an estimate one could then predict what defects may be anticipated if any, and would such defects warrent therapeutic abortion.

As stated previously, the critical time in organogenesis can be roughly estimated to occur during a relatively few days specifically for each organ and thus the type of defect most likely to result can be predicted. Therefore, the greatest problem is in predicting the

probability that such an organ will be defective. In predicting any probability one must rely on experience in the past. This is why the incidence of abnormal outcome of maternal rubella is important. If a very large number of cases were known in which the percentage of abnormal outcome was recorded, a physician could then predict with moderate accuracy the chance of an affected child being born to the specific case of maternal rubella confronting him.

Since the time of onset of symptons of a viral infection seems all important as a teratogenic factor, the narrower the time limit the better the accuracy of prediction. However, when one limits the time factor, he also limits the number of cases known for each interval.

In a review of the literature, only five reports were found giving the approximate percentage of abnormal outcome of maternal rubella in intervals of four week periods and all of these were published since 1960, (see table III). Likewise the number of cases reported is limited and thus the statistical significance should be viewed with caution. As would be expected, the greatest incidence of abnormal outcome appears to be in the first four weeks (54%) and decreases rapidly as the gestational period lengthens. Incidences were not reported in four week intervals after the first trimester since these authors felt this to be the most critical period.

Table III

Incidence of abnormal outcome of maternal rubella.

Inclusive of: spontaneous abortion
still born
congenital defect
neonatal deaths
Exclusive of: therapeutic abortions
prematurity

weeks	author	total # of cases reported	#normal births	% of abnormal
1-4 weeks	Pitt	55	26	53%
	Lock	6	3	50%
	Mullins	5	0	100%
	Michaels	35	18	47%
	Siegel	10	2	80%
	TOTAL	111	49	54%
5-8 weeks	Lock	14	10	29%
	Mullins	3	1	67%
	Michaels	44	36	22%
	Siegel	41	18	56%
	TOTAL	102	65	36%
9-13 weeks	Lock	19	14	26%
	Mullins	3	2	33%
	Michaels	49	46	7%
	Siegel	53	42	21%
	TOTAL	124	104	16%

Summary

A discussion of the clinical symptoms of rubella is presented followed by a brief consideration of the teratogenic factors influencing organogenesis during the first 12 weeks of pregnancy. A review of several articles was made and the incidence of abnormal outcome of maternal rubella reported by these authors is compounded for their results. A total of 609 cases of maternal rubella in the first trimester resulted in about 31% abnormal outcome of the fetus compared with about 3 1/2% for the last two trimesters. This review was carried further to include incidence of abnormal outcome of maternal rubella for each 4 weeks of gestation during the first trimester.

The incidence of abnormal outcome when rubella was contracted during the first 4 weeks of gestation, was found to be about 54%; during the second 4 weeks, about 36%; and during the last 4 weeks of the first trimester, about 16%.

Also mentioned are some of the factors influencing incidence, and the need for caution in interpreting results.

Conclusion

1. Rubella may be expected to produce fetal damage when contracted during the first 12 weeks of pregnancy.
2. The incidence of abnormal outcome following maternal rubella appears to be highest when the rubella is contracted during the first 4 weeks of pregnancy and thereafter deminishes as progestation period increases.
3. The incidence of abnormal outcome of maternal rubella when contracted during the last 2 trimesters is similar to the incidence of abnormal outcome of pregnancies with no known history of the disease.
4. Data on risks to the fetus as a result of maternal rubella should be calculated on the basis of weeks, rather than trimesters, in which the onset of the illness in the pregnant woman occurs.
5. The development of rubella prior to the eighth week of pregnancy may be considered an indication for therapeutic abortion since there is more than a one third chance of abnormal outcome.
6. Follow up studies are extremely important in arriving at the incidence of congenital anomalies.
7. One should view with caution any data on frequency of congenital defects becuase of the variability in limitations observed in reporting.

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