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Assisted Reproduction Versus Spontaneous Conception: A Comparison of the Developmental Outcomes in Twins

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ABSTRACT. The use of assisted reproductive technology is increasing rapidly. Research, although sparse, has resulted in inconsistent findings as to the developmental prognosis for infants conceived by assisted reproductive techniques such as in vitro fertilization and the use of fertility drugs. In the present study, the authors compared twins who were spontaneously conceived with those who were conceived through assisted reproductive technology. The authors found differences in birth weight and gestational age. Infants conceived by assisted reproductive technology fared worse than did those who were spontaneously conceived. The authors found no differences between the groups in mental development at 24 months of age, but they found evidence of differences in physical development. Implications of the findings are discussed.

Key words: development; twins; assisted reproduction

IN RECENT DECADES there has been an explosion in the use of assisted reproductive technologies such as in vitro fertilization and the use of fertility drugs (Golombok, Bhanji, Rutherford, & Winston, 1990; Hahn, 2001; Russell, Petrini, Damus, Mattison, & Schwarz, 2003; Shiono & Behrman, 1995) yet, in comparison, the research that has been conducted to ascertain if and how different modes of conception may impact resulting offspring, is still in its early stages. Initially, researchers expressed concern about the outcomes of children conceived by alternative methods, and the rationale was primarily medical and biological in scope (Levy-Shiff et al., 1998).

Because of these early concerns, researchers have conducted studies to address a wider range of outcome data. Some researchers have analyzed birth information such as gestational age and birth weight. Both of these characteristics are important because they tend to predict later health and educational problems (Paneth, 1995). A database exists (Golombok, Cook, Bish, & Murray, 1995; Golombok, MacCallum, & Goodman, 2001; Golombok, MacCallum, Goodman, &

Rutter, 2002; Hahn, 2001; Levy-Shiff et al., 1998) that researchers can use to investigate overall family functioning after assisted reproduction. In addition, the socioemotional functioning of the children has been a target of research. A smaller database provides information about the children's cognitive functioning (Brandes et al., 1992; Golombok & MacCallum, 2003; Levy-Shiff et al.). All of that information is important to couples that are attempting to make more informed decisions about the use of reproductive technologies.

Family and Socioemotional Development

Researchers have suggested that information about family functioning is generally conclusive and positive in its findings. That is, families that include children conceived by reproductive technologies were at least as well adjusted as were families with children conceived by natural methods (Golombok, Cook, Bish, & Murray, 1995; Golombok, MacCallum, & Goodman, 2001; Golombok, MacCallum, Goodman, & Rutter, 2002; Hahn, 2001). In fact, some advantages may be present in the former group, such as more positive relationships reported between parents and children and higher degrees of maternal warmth and emotional involvement (Golombok et al., 1995; Hahn).

Socioemotional functioning in children conceived by reproductive technologies also has been examined, and the results produced varied findings. Hahn (2001) reported that the majority of studies found no difference between the two groups of children, with the exception that more behavioral and social difficulties were found in children conceived through reproductive technology (Golombok et al., 1990; Levy-Shiff et al., 1998) than were found in those children conceived by spontaneous reproduction.

Information about family functioning and social emotional outcomes for children is valuable for couples considering assisted reproduction. The research is still not extensive; nevertheless, it provides a generally supportive position (with a few exceptions) for using reproductive technology. However, the physical and cognitive outcomes for children conceived with reproductive technologies are less c]ear. Therefore, more studies are needed to determine if the offspring of such technologies are at risk for physical and cognitive consequences, long-tern developmental consequences, or both.

Physical Development

Our review of existing studies of physical development in children conceived with reproductive technologies indicated inconsistent findings. The authors of one study conducted in Israel (Brandes et al., 1992) provided a systematic analysis of several developmental indexes of children conceived by in vitro fertilization (IVF) and of those who were conceived by spontaneous reproduction. The authors reported that their study was the first to use a matched-control group of children who were not conceived by use of medical intervention of any kind. They also provided one of the few longitudinal studies of the outcomes associated with assisted reproduction. On the basis of their results, they suggested that differences were found in birth weight and gestational age, with the infants conceived by IVF faring lower on

both indexes than those who were naturally conceived. Yet children conceived by IVF showed no developmental delays and scored in the average range when compared in terms of physical development with matched peers at 22 months of age.

Dhont, De Sutter, Ruyssinck, Martens, and Bekaert (1999) found similar results in their large-scale study of singleton and twin births in Belgium. The authors compared infants on several developmental indexes at birth, including gestational age and birth weight. They found differences in gestational age between the singleton pregnancies conceived by assisted reproductive technologies and those that were not. No differences were found on either measure for twin births.

Other smaller studies have found similar results with regard to birth weight and gestational age. Fitzsimmons, Bebbington, and Fluker (1998) hypothesized that twins conceived by assisted reproductive technologies would fare better than would twins from spontaneous pregnancies, but their hypothesis was not supported. No differences were found between the two groups. Those findings were supported for twins but not for singletons in subsequent studies (Addor, Santos-Eggimann, Fawer, Paccaud, & Calame, 1998; Minakami et al., 1998). In addition, Saunders, Spensley, Munro, and Halasz (1996) did not find differences in birth weight between the two groups when matched for gestational age.

Although several available studies revealed no differences in birth characteristics, there was an exception. Nyirati, Orvos, Bartfai, and Kovacs (1997) found negative physical outcomes for infants conceived by assisted reproductive techniques, and the impact was worse for multiple births. Long-term differences, however, were not evident at 2 years of age.

Cognitive Development

A final area of interest to investigators has been the examination of the effects of reproductive technology on the cognitive development of offspring. In their review of existing research, Golombok and MacCallum (2003) concluded that most of the studies showed no differences between the two groups of children in the domain of cognitive development. The authors did, however, suggest that more research would be needed to draw definitive conclusions.

In their review of studies in that area, Golombok and MacCallum (2003) found that, in general, no differences were found between the two groups in the domain of cognitive functioning. The results of another study of 102 children (51 singletons conceived naturally and 51 singletons conceived by assisted reproduction) in Israel revealed no statistically significant differences between the two groups on the Israeli version of the Wechsler Intelligence Scale for Children-Revised (Levy-Shiff et al., 1998). One of the assisted reproduction groups (in vitro fertilization-embryo transfer) had intelligence test scores that were higher than those for the control group, but the difference was not significant. Levy-Shiff et al. suggested that higher quality parenting might be the reason for the difference.

Brandes et al. (1992) also examined cognitive development in children conceived by reproductive technologies. Those authors used the Bayley Scales of Infant Development and the Stanford-Binet Intelligence Scales to measure cognitive functioning. At 22 months of age, children who were conceived naturally had scores that were similar to those who were conceived with reproductive technology. That result suggested no significant differences between the two groups.

Summary of the Available Literature

In light of the early findings regarding the effects of assisted reproductive techniques on birth characteristics of the offspring (and the suggestion by other researchers that more work needs to be done before the field establishes its conclusive position), our purpose in the present study was to further clarify the relationship between natural versus induced conception methods (e.g., fertility drugs, in vitro fertilization) and the developmental outcomes of those children. According to one source, 25% to 30% of pregnancies that used assisted reproduction techniques result in multiple births (Santrock, 2000). Therefore, because of the high percentage of multiple births, we used data from low-birth-weight twins, both at birth and at long-term follow-up evaluations.

The Present Study

Our overall focus in this study was to compare twins who were conceived naturally with those whose conception was induced by assisted reproductive techniques. We controlled for the potential developmental risks of multiple births. Although other investigators have conducted similar research, the findings still need further replications (Levy-Shiff et al., 1998). Moreover, the research on cognitive functioning outcomes has been conducted in a variety of countries and the generalizability of the findings to U.S. samples needs to be determined.

Because of the serious risk factors associated with low-birth weight and shorter gestational age, we compared two groups of children (i.e., those conceived by spontaneous reproduction and those conceived by reproductive technologies) on characteristics at birth. We also sought to understand the long-term effects that the method of conception may have on children. Because of the characteristics at birth, a child may be at risk developmentally. Therefore, we also included in our study a group of children who were evaluated at a neonatal intensive care unit (NICU) follow-up clinic at 24 months of age to compare the two groups' weight, mental development, and physical development indexes.

Method

Participants

Participants in the present study included mothers and their twin children. A total of 60 mothers representing 120 children participated. The mothers ranged in age from 20 to 39 years

old (M age = 30.78 years, SD = 3.87). The mothers in the assisted reproductive technology group (M age = 32.29 years, SD = 3.32) were significantly older than were those in the group who conceived naturally (M age = 30.13 years, SD = 3.99; t(110) = -2.77, p < .007). Fifty-seven of the participants were married, one was single, and the remaining two reported unspecified marital status. Forty-five of the mothers were from European-American backgrounds. Data were missing on race, ethnicity, or both items for the remaining 15 participants. Thirty-nine mothers conceived naturally, 18 used assisted reproductive technology (more specific information about the particular type of intervention was not available), and 3 participants used unspecified types of conception. We eliminated that latter group from subsequent analyses. Twenty-nine of the participants gave birth by vaginal delivery, and 29 participants gave birth by Caesarian delivery. Data were missing on delivery type for the remaining two participants. (More information is available in the Results section.)

A subset of those same children (n = 40) was referred for follow-up care at a NICU. Follow-up care was available for those children who met specific criteria (i.e., birth weight less than 1,500 grams, mechanical ventilator support required for more than 3 days, infants requiring home oxygen therapy or exchange transfusion, perinatal distress as indicated by Apgar scores of less than 6 at 5 min, twin of an infant meeting any of the referral criteria, grade II-IV Intraventricular Hemorrhage, or physician request). Parents brought their children to a NICU follow-up clinic when children's corrected age was 24 months.

Procedure

We obtained names of potential participants from a list of all women (N = 702) who gave birth to live twins from 1993 to 1997 at a local hospital. We randomly selected a total of 150 mothers' names from that list. We sent letters describing the present study to the mothers and requested their permission for confidential access to their medical files and those of their children. We sent a second mailing to the mothers from whom we did not receive a response.

The next phase of the study involved collecting data from the hospital and NICU follow-up clinic records. The infants' birth records provided information about birth weight and gestational age. We obtained additional data for the group that was involved with a NICU follow-up clinic. As part of the clinic visit, children received a thorough physical examination. Thus, a child's weight at each visit was readily accessible. Furthermore, clinicians administered both the Mental and Motor Scales from the Bayley Scales of Infant Development-Second Edition (BSID-II; Bayley, 1993) to all of the children. We obtained the Mental Developmental Index (MDI) and Physical Developmental Index (PDI) for each child. We selected the BSID-II because it is a reliable and valid instrument for measuring mental and physical development in very young children, and it is essentially the test of choice when evaluating those skills in children who are 24 months of age or younger (Sattler, 2001).

Data Analyses

We analyzed the data by using the SPSS-PC computer program. We used one-way analyses of variance and covariance (ANCOVA) to compare the infants who were conceived naturally with those whose conception was induced on the variables of interest. We carefully inspected tests of the assumptions of linearity and homogeneity of variance because of unequal sample sizes across groups and found them to be satisfactory (Keppel, 1991). Because the mothers' ages differed significantly between the two conception method groups, we calculated correlations between mothers' age and each dependent variable. When the dependent variable correlated significantly with mothers' ages, we used ANCOVA's with age of the mother as the covariate.

Results

Child Characteristics at Birth

Results of comparisons are presented in Table 1. An examination of mean birth weight (adjusted for mother's age) and of gestational age revealed that infants who were conceived spontaneously had significantly higher birth weights, as well as significantly higher gestational ages, than did infants whose conception was induced, $p < .001$.

Follow-Up Clinic Data

Results of comparisons are presented in Table 1. An examination of means revealed that infants who were conceived spontaneously were not significantly different from those whose conception was induced by assisted reproductive techniques in terms of weight at 24 months of age, $p > .05$, or on the MDI, $p > .05$. An examination of means did reveal significant differences, $p < .05$, between the two groups on the PDI, though.

Discussion

Our purpose in this study was to add to the emerging body of literature addressing the developmental outcomes of offspring conceived by assisted reproductive technology. We used psychometrically sound and supported instruments and included a comparison group. Our results suggested that the method of conception may play a role in birth weight and gestational age. Our results also indicated that physical development at 2 years of age varies as a function of method of conception. That is, children whose conception was induced by assisted reproductive technology had significantly lower PDI scores than did children whose conception was natural. Because only twin pairs participated in the present study, we ruled out single births or other multiple births as an explanatory factor for our findings.

Assisted reproductive techniques may be related to the probability of multiple births, and it appears as if these techniques also may be associated with the likelihood of early gestational age and its correlate--low birth weight. Therefore, the main purpose of that aspect of the present study was to confirm previous studies (Addor et al., 1998; Dhont et al., 1999;

Fitzsimmons et al., 1998; Minakami et al., 1998; Saunders et al., 1996) and to add to the growing amount of empirical research addressing developmental outcomes for different forms of conception.

Researchers have found that infants with low birth weight are at a higher risk for a range of developmental outcomes than are infants with average birth weights. These outcomes may include future learning problems, cerebral palsy, and vision and hearing problems (Paneth, 1995). Consequently, if children conceived by artificial means are at higher risk for low birth weight, they in turn are at higher risk for any of the problems associated with the condition.

In the present study, we found no differences between the two groups of children in mental development at 24 months of age. Thus, even though the children whose conception was induced had lower birth weights within the first 2 years of life, their mental development did not appear to be impacted by this technology. In contrast, physical development at this same age appeared to be related to the type of conception. The findings from the present study are especially noteworthy because significant differences were detected in a relatively small sample. The findings in our study replicated a portion of the findings of Brandes et al. (1992) and Nyirati et al. (1997), who found lower birth weights and gestational ages for children conceived by IVF. Similarly, those studies reported no differences in mental development at approximately 2 years of age. Both studies used the BSID-II as a measure of mental development and found similar results.

Discrepant results, however, occurred with physical development when differing measures were used. Brandes et al. (1992) and Nyirati et al. (1997) showed no differences between the two groups of children, whereas in the present study, we found that naturally conceived children had higher physical-development scores at 24 months old than did those conceived with reproductive technologies. More general and global measures of physical development, such as weight, were used in the earlier studies. When comparing the global measure of physical development in our study, we found no differences between groups at 24 months of age. The differences occurred when more specific information was gathered about physical development (i.e., PDI scores). Therefore, more subtle aspects of physical development may be related to differing types of conception. More research will be needed to confirm these results, and this is an area of study worth pursuing. No other researchers have used the PDI score from the BSID--II in their research.

In addition, a psychometric explanation for the results suggested that the nature of the testing may have influenced the findings. Researchers use corrected ages when calculating scores for the BSID-II. By adjusting for prematurity, the children who were conceived by assisted reproduction may be similar to their counterparts who were conceived naturally. Adjusting for prematurity ends at 24 months of age, and researchers have suggested that children who are born prematurely have higher propensity for long-term academic problems (Paneth, 1995). Therefore, once the adjustment for prematurity ceases, differences may emerge--as occurred in the present study.

The follow-up clinic component of our study uncovered differences in physical development at 24 months of age, as measured by the BSID-11. Because we did not use the adjustment for prematurity in this study and we had a small population size, this finding is especially noteworthy. The physical scale from the BSID-II assesses fine and gross motor skills. Taken together, the findings from the developmental measures suggest that type of conception has a stronger relationship with physical development rather than with mental development. The physical environment of the mother also may have influenced this finding. Those women who have difficulty conceiving may provide a weaker physical environment for the developing fetus, and the nature of the environment may impact physical development more than it impacts mental development (Levy-Shiff et al., 1998). Furthermore, the environment after birth may be more conducive to promoting mental development (Golombok et al., 1995).

Several limitations are inherent in this type of research. The follow-up clinic population size was small. Furthermore, we did not know the specific type of assisted reproduction. Future researchers should address that aspect. Another limitation in conducting research of this nature is the limited pool of participants. More often, parents with higher socioeconomic status have the resources for assisted reproductive technologies. Because of this limitation, the participants in the present study may not be representative of the population at large. Therefore, these findings should be interpreted with caution. Furthermore, this area of research is still in its early stages, and more studies are needed to address this important aspect of human reproduction.

Because of the scant amount of research conducted in this area, many more studies are necessary. We hope that our investigation will prompt others to conduct similar studies, which will expand on our methods. One suggestion is that future investigators separate the different types of assisted reproduction techniques to determine if different techniques lead to different developmental outcomes. Future investigators should expand the participant characteristics. Furthermore, more longitudinal studies, which follow the children into school age and determine if differences in educational performance exist, should be conducted. Other developmental outcomes such as language, health risks, and social and emotional growth also deserve further investigation. Studies of the impact of educational and medical interventions also will be critical.

In conclusion, we found differences in birth characteristics in children conceived naturally versus those conceived by assisted reproductive techniques. We did not find differences in mental development at a 2-year follow-up; however, the children conceived by assisted reproductive-technologies demonstrated lower scores on a measure of physical development at 2 years of age. This area of research is important to families who are making decisions about using assisted reproductive technologies.

TABLE 1. Means and Standard Deviations for Natural and Induced Birth Groups

| | Method of conception | | | | | | |
| | Natural | | Induced | | | | |
Dependent variables	M	SD	M	SD	df	F value	η^2
Birth characteristics							
Birth weight (g)	2009.99	585.47[a]	1476.94	543.55[b]	1, 109	17.03**	.14
Gestational age (weeks)	33.56	3.25[a]	30.41	3.45[b]	1, 110	21.51**	.16
Follow-up clinic data (at 24 months of age)							
Weight (g)	5547.43	539.77[c]	5606.4	752.96[d]	1, 30	.04	.001
MDI	93.58	15.28[e]	92.25	11.47[f]	1, 28	.14	.005
PDI	99.89	18.53[e]	85.25	19.26[f]	1, 28	4.46*	.13

Note. MDI = Mental Developmental Index; PDI = Physical Developmental Index.
[a]n = 78. [b]n = 24. [c]n = 20. [d]n = 12. [e]n = 19. [f]n = 12.
*p < .05. **p < .001.

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