Neurodevelopment of Children Prenatally Exposed to Selective Reuptake Inhibitor Antidepressants:
Toronto Sibling Study

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ABSTRACT

Background: The reproductive safety of selective reuptake inhibitor (SRI) antidepressants needs to be established to provide optimal control of maternal depression while protecting the fetus.

Objective: To define a child's neurodevelopment following prenatal exposure to SRIs and to account for genetic and environmental confounders in a sibling design using the Toronto Motherisk prospective database.

Method: Intelligence and behavior of siblings prenatally exposed and unexposed to SRIs were assessed by using the Wechsler Preschool and Primary Scale of Intelligence–Third Edition, Child Behavior Checklist, and Conners Parent Rating Scale–Revised and subsequently compared. Mothers, diagnosed with depression using *DSM-IV*, were assessed for intelligence quotient (IQ) and for severity of depressive symptoms with the Center for Epidemiologic Studies Depression scale. Prenatal drug doses and durations of exposure, child's age, child's sex, birth order, severity of maternal depression symptoms, and Full Scale IQ, the primary outcome measure, of both the mother and the child were considered in the analyses.

Results: Forty-five sibling pairs (ages 3 years to 6 years 11 months, prenatally exposed and unexposed to SRIs) did not differ in their mean ± SD Full Scale IQs (103 ± 13 vs 106 ± 12; $P = .30$; 95% CI, −7.06 to 2.21) or rates of problematic behaviors. Significant predictor of children's intelligence was maternal IQ ($P = .043$, $\beta = 0.306$). Severity of maternal depression was a significant predictor of Child Behavior Checklist Internalizing ($P = .019$, $\beta = 0.366$), Externalizing ($P = .003$, $\beta = 0.457$), and Total scores ($P = .001$, $\beta = 0.494$). Drug doses and durations of exposure during pregnancy did not predict any outcomes of interest in the exposed siblings.

Conclusions: SRI antidepressants were not found to be neurotoxic. Maternal depression may risk the child's future psychopathology. The sibling design in behavioral teratology aids in separating the effects of maternal depression from those of SRIs, providing stronger evidence in clinical decision-making.

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Maternal depression in pregnancy is associated with adverse pregnancy outcomes for both mother and child and with very high rates of postpartum depression. Up to 16% of pregnant women with depression require pharmacotherapy.[1] Selective reuptake inhibitors (SRIs) are commonly used to treat depression in pregnancy. The child's long-term neurodevelopment following prenatal SRI exposure, an essential part of reproductive drug safety research, is not clearly defined. Selective reuptake inhibitors may have the potential to interfere with the developing fetal central nervous system. Serotonin and norepinephrine are known to significantly influence the process of brain development.[2] The axons of serotonergic neurons project to every part of the central nervous system, where they impact neuron activity, and play an essential role in the integration of cognition and behavior. The disruption of this process may result in permanent alterations of brain functioning.[2]

Research in behavioral teratology is expensive, time-consuming, and complicated by multiple confounders, with genetics among the most challenging to control for. Genetic and environmental factors both are strongly associated with child intelligence and behavior,[3,4] and the complex interplay of these 2 influences significantly complicates neurobehavioral studies. Twenty-five years of research on antidepressants in pregnancy have failed to uncouple the effects of antidepressants from maternal depression (a genetic and potentially environmental confounder) on prenatally exposed children.[5] Therefore, implementing an appropriate study design may play an integral role in accounting for these effects.

To separate genetic and environmental influences, we employed a novel design in drug safety research, which directly compared long-term cognitive and behavioral outcomes of siblings exposed and unexposed to SRI antidepressants during gestation. On the basis of previous research yielding reassuring cognitive results in studied children,[6,7] we hypothesized that no effects of SRI exposure would be observed and no differences would be found between the groups. Additionally, other potential predictors of the outcomes of interest were examined.

METHOD

Participants

Mothers were selected and recruited from the prospectively collected database of Motherisk (an information and consultation service for women and their health providers on the reproductive risk/safety of environmental and genetic

Clinical Points

- The need of pharmacotherapy for prenatal maternal depression creates a conflict between maternal well-being and the potential teratogenicity of selective reuptake inhibitors (SRIs) if their reproductive safety is not established.
- This sibling design study helped to separate the effects of SRI medications from the effects of maternal depression and revealed no differences in Full Scale IQ and rates of problematic behavior in siblings discordant for prenatal exposure to antidepressant medications.
- These findings from the Toronto Sibling Study provide stronger evidence for the reproductive safety of SRIs and should be considered in clinical decision-making for treatment of maternal depression in pregnancy with SRIs.

factors) at The Hospital for Sick Children in Toronto, Canada. Pregnant women who sought counseling on the safety of SRI medications answered a standardized database questionnaire that required information on their demographics and medical and social histories. Verbal consents for pregnancy follow-up and research participation were obtained at the initial call to Motherisk followed by a written consent after maternal acquaintance with study details.

Women diagnosed with depression using *DSM-IV* criteria and their 2 children, exposed and unexposed to selective serotonin and/or serotonin-norepinephrine reuptake inhibitor antidepressants (SRIs, as an umbrella term), were included and constituted the 2 study groups. Only siblings whose difference in age did not exceed 3 years were included in order to apply the same psychological tests.

Excluded were mothers on psychotropic drug polytherapy for comorbid psychiatric conditions, known teratogens (eg, antiepileptic drugs, isotretinoin) or substances of abuse (eg, alcohol) and mothers and their children with inadequate English proficiency or medical conditions, unrelated to in utero exposure to SRIs, that may affect child cognitive outcomes (eg, postnatal head trauma, encephalitis).

The primary outcome measure was child Full Scale IQ (a combination of Verbal and Performance IQs), which is a strong predictor of the child's cognitive performance and future quality of life and has a clearly defined standard deviation of 15. To achieve 80% power, a sample size of 34 sibling pairs was determined to be needed to detect a clinically significant mean difference of half a standard deviation (ie, 71/2 IQ points), with $\alpha = .05$ and $\beta = 0.20$ (http://www.biomath.info/power/prt.htm). Considering the importance of behavioral outcomes in children of mothers with depression, the Child Behavior Checklist (CBCL)[8] and Conners Parent Rating Scale–Revised (CPRS-R)[9] were also obtained.

This study was approved by the research ethics board at the Hospital for Sick Children.

Procedures

Initial information about maternal medical, genetic, and obstetric health and medication use (eg, antidepressants, other concomitant psychotropic drugs, and drugs of abuse) was obtained at the time of the first call to Motherisk, as per standard database intake form. To reduce recall bias, a routine telephone follow-up of children 6 to 9 months after delivery was performed. Also obtained were details on pregnancy course, medication use during pregnancy, delivery methods, postnatal complications, medication change, and breastfeeding status. At the time of psychological testing, the child's anthropometric measurements, such as height, weight, and head circumference, as well as additional medical information provided by the mother, were obtained. Additionally, after receiving maternal written consent, children's medical reports were requested from their attending pediatricians.

Assessment of Maternal Depression

Information on maternal depression was collected at (1) the initial contact to Motherisk, (2) the routine follow-up at 6 to 9 months postpartum, and (3) the maternal and child testing. The severity of maternal depression during pregnancy and the severity and number of depressive episodes after delivery were assessed using the 10-point visual analog scale (VAS)[10] for each episode (with 10 reflecting the most severe depression symptoms). This test has also been validated in the assessment of severity of depression in our previous publications.[7,31,32] At the hospital visit, the mother filled in a Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report scale designed to measure depressive symptoms.[11] The CES-D scores from 0 to 60, with a cutoff of 16, which represents clinically significant depressive symptoms. Also obtained were parental socioeconomic status, measured using the Hollingshead Four-Factor Index of Social Status,[12] and household income, rated on a 5-point scale.

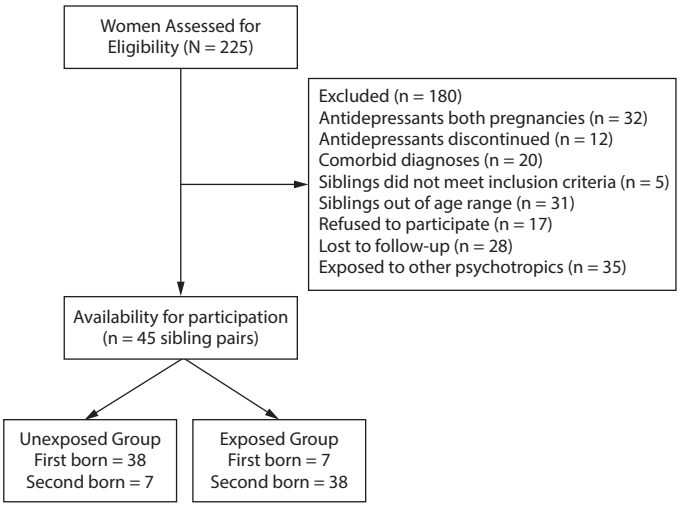
Intellectual and Behavioral Assessments

Psychological assessments were performed at the psychology laboratory at the Hospital for Sick Children in Toronto. A psychometrist masked to group affiliation tested all children individually using age-appropriate standardized psychological tests and routinely documented and commented on each child's behavior.

Children's intelligence was evaluated using the Wechsler Preschool and Primary Scale of Intelligence–Third Edition (WPPSI-III).[13] This test provides 3 composite scores: Full Scale IQ, which measures general intellectual functioning; Verbal IQ, which measures verbal reasoning and comprehension; and Performance IQ, which measures fluid reasoning, spatial processing, attentiveness to detail, and visual-motor integration.

Maternal intelligence was evaluated using the Wechsler Abbreviated Scale of Intelligence (WASI),[14] which also yields Full Scale, Verbal, and Performance IQ scores. Child behavioral problems were assessed using 2 maternal-report questionnaires: the CBCL[8] and the CPRS-R.[9] Children were classified as having normal or clinically elevated test results based on whether their *T* score was less than or above 65 on the CBCL and less than or above 64 on the CPRS-R. Results from 3 global CBCL scales (Internalizing Problems, Externalizing Problems, and Total Problems) and 2 CPRS-R

Figure 1. CONSORT Diagram of Mothers and Their Children Who Were Exposed and Unexposed to SRIs In Utero



scales (Global Index and *DSM-IV* symptom subscale) were examined.

Statistical Analysis

Data analyses were conducted using SAS version 9.3 software (SAS Institute Inc, Cary, North Carolina). Descriptive statistics were used in order to apply proper statistical tests. The paired *t* test was used to compare sibling pairs on all continuous variables, such as intelligence subtests and tests scores, exposure to depression and antidepressants during pregnancy, pregnancy course, and perinatal outcomes. Chi-square analyses were used to assess categorical variables such as sex and whether children obtained normal or clinically elevated behavior problem scores. All analyses were 2-tailed, with $P \leq .05$ considered to be significant.

Bivariate associations were performed between each predictor and each outcome for the entire sample. The predictors evaluated were child's age, child's sex, birth weight, birth order, maternal IQ, severity of depression during pregnancy, maternal depression at time of child testing (CES-D), and number and severity of depressive episodes after delivery. In the exposed sibling group, simple linear regression analyses served to evaluate the impact of the potential predictor variables on the child's IQ indices, with emphasis on the extent of exposure to antidepressants (dose and duration) during pregnancy. A multivariable mixed model, to account for the paired nature of the data, was used to further examine the intelligence outcomes, while we further adjusted for the effects of child's age, birth order, and severity of maternal depression during pregnancy and after delivery.

RESULTS

Figure 1 provides a CONSORT diagram of the current sample. Of the 225 pregnant women who called Motherisk from 2005 to 2008 inquiring about the reproductive safety of the SRIs they were taking and reporting a previous delivery, 32 were excluded who reported antidepressant exposure in both pregnancies and 12 were excluded who discontinued their medications prior to conception in both pregnancies. Additionally, 20 women were excluded due to comorbid medical conditions, such as hyperthyroidism and seizures, while 35 were excluded because of exposure to other psychotropic medications. Additionally, 36 potential siblings were unsuitable because their ages were out of range for the psychological tests (n = 31) or they did not meet inclusion criteria (eg, infections, epilepsy; n = 5). Finally, 17 women refused participation, and 28 families were lost to follow-up. The final sample therefore consisted of 45 sibling pairs and their mothers. The demographic and medical information of the women who declined to participate, or were lost to follow-up, was analyzed. These women were not different from those included in any parameters tested.

Women were exposed to citalopram, paroxetine, sertraline, fluoxetine, and venlafaxine, and their defined daily doses ranged from 0.38 to 3.00. For the 45 pregnancies with antidepressant exposure, 7 were exposed in the first trimester only, 1 in the first and second, 1 in the second only, 7 in the second and third, 3 in the third only, and 26 throughout gestation. The median duration of antidepressant use during pregnancy was 36 weeks (range, 4 to 42 weeks). Mothers taking antidepressants reported more severe depressive symptoms during pregnancy, but differences in their scores did not reach statistical significance ($P = .07$; 95% CI, −0.10 to 1.97) (Table 1). The CES-D scores revealed that approximately 30% of the mothers were experiencing clinically significant depressive symptoms.

Mean maternal IQ was 109 ± 10.7 (Table 1). Household annual income was reported as equal or more than $50,000 in 86.4% of families.

Children ranged in age from 3 years to 6 years 11 months. Exposed children had a slightly shorter length of gestation than their unexposed siblings (mean difference = 5 days)

Table 1. Maternal Characteristics of 45 Women

Variable	Exposed Siblings (n = 45)	Unexposed Siblings (n = 45)	95% CI	*P* Value
Weight gain during pregnancy, mean (SD), kg	16.88 (7.4)	16.28 (6.4)	−1.50 to 2.70	.56
Duration of depression from onset until time of child testing, mean (SD), y	8.10 (4.8)	7.75 (5.1)	−0.08 to 0.78	.11
Severity of depression during pregnancy (on 1–10 VAS), mean (SD)	3.51 (2.8)	2.58 (3.0)	−0.10 to 1.97	.07
Cigarette use, n (%)	5 (11.1)	5 (11.1)		.97
Alcohol use, n (%)	0 (0.0)	0 (0.0)		
Standardized drug dose, mean (SD)	1.07 (0.7)			
	Mothers (N = 45)			
Full Scale IQ (WASI), mean (SD)	109 (10.7)			

Abbreviations: VAS = Visual Analog Scale, WASI = Wechsler Abbreviated Scale of Intelligence.

Table 2. Child Characteristics

Variable	Exposed Siblings (n = 45)	Unexposed Siblings (n = 45)	95% CI (lower to upper)	*P* Value
Male, n (%)	22 (48.9)	28 (62.2)		.20
Firstborn, n (%)**	7 (15.6)	38 (84.4)		< .001
Gestational age, mean (SD), wk*	39.24 (1.5)	39.90 (1.5)	−1.31 to −0.02	.04
Birth weight, mean (SD), g	3,535.17 (453.6)	3,526.49 (449.7)	−170.57 to 187.92	.92
Height percentile, mean (SD)	51.33 (28.1)	54.68 (28.7)	−13.07 to 6.36	.49
Weight percentile, mean (SD)	57.20 (28.5)	60.27 (27.2)	−12.99 to 6.84	.54
Head circumference percentile, mean (SD)	58.36 (28.2)	55.97 (32.4)	−7.12 to 11.92	.61
Age at testing, mean (SD), months**	43.31 (10.1)	68.31 (10.2)	−29.62 to −20.38	< .001
Full Scale IQ, mean (SD)	103 (12.9)	106 (12.3)	−7.06 to 2.21	.30
Verbal IQ, mean (SD)	104 (11.9)	107 (12.8)	−7.48 to1.97	.25
Performance IQ, mean (SD)	101 (14.3)	103 (11.2)	−5.84 to 1.71	.28
CBCL internalizing problems, n (%)	5 (11.1)	3 (6.7)		.46
CBCL externalizing problems, n (%)	5 (11.1)	5 (11.1)		1.00
CBCL total problems, n (%)	6 (13.3)	4 (8.9)		.48
	Short Exposure (n = 11)	Long Exposure (n = 34)	95% CI (lower to upper)	*P* Value
Full Scale IQ, mean (SD)	103.1 (13.9)	103.5 (12.8)	−9.54 to 8.78	.93

*$P \leq .05$. **$P \leq .001$.
Abbreviations: CBCL = Child Behavior Checklist, CPRS-R = Conners Parent Rating Scale–Revised.

Table 3. Mixed-Model Analysis for Predicting Children's Full Scale IQ

Variable	β	*df*	*t*	*P*
Intercept	111.34	43	9.36	< .0001
Sibling group	−2.46	43	−0.56	.58
Severity of depression during pregnancy (on 1–10 VAS)	0.69	43	1.50	.14
Birth order	−2.49	43	−0.67	.51
Child's age at testing	−0.06	43	−0.44	.66

Abbreviation: VAS = Visual Analog Scale.

Figure 2. List of Wechsler Preschool and Primary Scale of Intelligence–Third Edition (WPPSI-III) Subtests Performed

VIQ	PIQ
Receptive Vocabulary Information Vocabulary Similarities	Block Design Object Assembly Matrix Reasoning

Abbreviation: PIQ = performance intelligence quotient, VIQ = verbal intelligence quotient.

(Table 2). Eighty-four percent of exposed children (38 of 45) were second-born, resulting in a statistically, significantly younger mean age compared to the unexposed group (Table 2). At the time of testing, the children did not differ in anthropometric measurements (Table 2).

No statistically significant differences were found between the exposed and unexposed siblings in the children's Full Scale or Verbal IQ scores and Performance IQ scores (Table 2). These results remained after adjusting for the covariates of interest (child's age, birth order, and severity of depression during pregnancy) in a mixed-model regression (Table 3). Full Scale IQ scores of children who were exposed to antidepressants in 1 trimester only (short exposure) were not statistically different from those of children exposed for 2 trimesters or throughout pregnancy (long exposure) (103.1 vs 103.5 respectively [$P = .93$; 95% CI, −9.54 to 8.78]) (Table 2). There were also no statistically significant differences in Verbal IQ and Performance IQ scores following short and long exposures. Moreover, there were no statistically significant differences between the 2 groups in the applied subscales (listed in Figure 2).

No statistically significant differences were seen between each group of children in terms of the proportions with

normal-range versus clinically elevated behavior problem scores on the 3 CBCL and 2 CPRS-R scales (Table 2). Severity of maternal depression during pregnancy was a significant predictor of CBCL Internalizing ($P = .019$, $\beta = 0.366$), Externalizing ($P = .003$, $\beta = 0.457$), and Total scores ($P = .001$, $\beta = 0.494$), as well as CPRS-R Global Index scores ($P = .044$, $\beta = 0.316$). Maternal depression at the time of testing was also a significant predictor for Internalizing ($P = .035$, $\beta = 0.319$) and Total scores ($P = .015$, $\beta = 0.363$).

After individually entering the variables of interest 1-by-1 in a simple linear regression analysis for the exposed group, we found that maternal IQ ($P = .043$, $\beta = 0.306$) and child's sex ($P = .045$, $\beta = 0.300$) were the only significant predictors for child's Full Scale IQ. Child's sex was also a significant predictor of Verbal IQ ($P = .030$, $\beta = 0.323$), and maternal Performance IQ of child's Performance IQ ($P = .021$, $\beta = 0.347$). For the exposed group, cognitive outcomes on the 3 IQ scales were not predicted by any of the variables: drug dose, duration of exposure during pregnancy, severity of maternal depression during pregnancy and at testing, number of depressive episodes after delivery, birth order, or admission to the neonatal intensive care unit.

DISCUSSION

In the present study, children who were prenatally exposed to SRIs did not significantly differ from their unexposed siblings in any measure of cognitive, behavioral, or physical development. Although twin studies are the gold standard for disentangling environmental and genetic effects, a twin design in drug safety studies is not a viable option since the ingested drug would reach both fetuses. Thus, the next best alternative is a sibling study design, which maintains a greater control of genetic and environmental influences. In the sibling design, the long-term neurocognitive outcomes of children prenatally exposed to a medication are compared to the outcomes of unexposed siblings, provided identical standardized tests wherein age-normed tests are used. Notably, sibling design also has the advantage of being time- and cost-efficient since fewer sibling pairs are needed to reach sufficient statistical power than with an independent pairs design. Sample size calculations showed that in order to compare the IQs of 2 independent groups, with a clinically significant difference of 7.5 points and 80% power, 62 children are needed per group. In our study, 45 sibling pairs assessed allowed us to achieve 90% power.

Nevertheless, sibling studies pose their own distinct challenges. Factors such as birth order,[15,16] family size,[16] and age of testing may contribute to differences in IQ scores between siblings. According to the Zajonc confluence model,[17,18] differences in the intellectual environments may account for the difference in the IQ of firstborns and younger siblings. Also, children from larger families achieved lower scores than those from smaller families, even when controlling for socioeconomic status. Therefore, we excluded families with more than 2 children and accounted for birth order statistically.

In the current study, the Full Scale IQ, Verbal IQ, and Performance IQ values of the exposed children were similar to those of their unexposed siblings, even considering that 85% of unexposed siblings were firstborn and were not necessarily exposed to maternal depression prenatally since the bulk of women developed depression postpartum, thus requiring antidepressant treatment during their second pregnancy. As a result, the majority of second-born children were exposed to maternal depression and antidepressant drugs, and by default, these children were significantly younger (on average) at the time of testing.

Neither intelligence nor behavioral outcomes in the exposed siblings were predicted by drug dose or exposure duration during pregnancy. Instead, maternal IQ significantly predicted child IQ, a phenomenon reported in numerous studies,[5,7,19] thus validating our findings. In addition, there were no differences in Full Scale IQ, Verbal IQ, and Performance IQ scores related to the extent and duration of prenatal SRI exposure (short, first trimester exposure vs long exposure throughout pregnancy). However, severity of maternal depression during pregnancy and at time of testing was a significant predictor of internalizing, externalizing, and total problems in CBCL and for CPRS-R . These findings were supported by Misri et al[20] and Bagner et al[21] who found that child internalizing behavior scores were predicted by perinatal maternal mood.

We also found that the gestational age of exposed neonates was shorter than that of the unexposed (39.2 vs 39.9 weeks). This slight difference, which is not clinically relevant, may be attributed to the more severe maternal depression during her exposed pregnancy, even while receiving pharmacotherapy. There is a significant body of evidence reporting an association between depression, associated stress, and shortened gestation.[22–28]

Siblings share many genetic traits and are exposed to similar family environments that contribute to child neurocognitive and behavioral development. The strengths of this study, therefore, include its ability to effectively control for genetic factors, antenatal and postnatal exposure to maternal depression, and shared environments and to separate the effects of antenatal exposure to antidepressants. Moreover, the sibling design demands a smaller cohort and is cost-effective.

We should admit the limitations of this study related to use of maternal self-report on severity of depression during pregnancy and after delivery; however, we used the visual analog scale, which was shown to be accurate despite lower sensitivity[29] and shown to correlate with standard categorical 5-grade scale test results.[30] Another potential bias may be associated with maternal self-report on potential exposure to teratogens during her pregnancy unexposed to SRIs. Considering that the included children did not present with birth or cognitive defects, this bias, if present, is minimal. Another limitation is the potential recall bias associated with the child's time of testing at ages 3 years to 6 years 11 months (the retrospective part of this design). However, the 6- to 9-month telephone follow-up minimizes this recall

bias. Finally, while the severity of maternal depression may influence the mother's responses when filling out child behavior questionnaires (CBCL, CPRS-R), bias is minimized as mothers evaluate the behavior of both her exposed and unexposed children simultaneously. Due to the number of younger children included, a teacher report could not be gathered for the entire cohort.

In conclusion, SRIs were not found to be neurotoxic in the assessed cohort of siblings discordant for in utero exposure. Maternal depression was a significant predictor of the child's problematic behavior, pointing to the increased risk for future child psychopathology and the need for perinatal depression control. The sibling design provides an additional control for genetic and environmental factors and stronger evidence for clinical decision-making in the treatment of depression in pregnancy. Future studies in reproductive toxicology should utilize the sibling design in prospective research.

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Drug names: citalopram (Celexa and others), fluoxetine (Sarafem and others), isotretinoin (Amnesteem, Zenatane, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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Additional information: The Motherisk website can be found at www.motherisk.org. The clinical Motherisk database was used for the study cohort recruitment, but it cannot be accessed by readers due to confidentiality.

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