both surgical procedures are important factors that could lead to impaired healing of uterine scar, uterine rupture, and impaired placentation (placenta accreta) in the next pregnancies.1,3

While there is no evidence that locking the second layer is related to impaired healing of the uterine scar, it is, to our knowledge, an unusual procedure that has not been reported in literature. With all our respect, we are skeptical that this could be a common practice, as we do not understand why a surgeon would do this.

To our opinion, beside good surgical principles, there are 3 modifiable factors that have been interrelated and that can be implicated in long-term impaired healing of the uterine scar: a single-layer; the inclusion of endometrium (decidual layer of the uterine wall); and the locking of the first layer. The actual literature suggests that a combination of the 3 (a locked single-closure of the uterus including the full thickness of the myometrium with the endometrium into the scar) is detrimental for future pregnancies’ outcomes when compared to the unlocked double-layer closure aiming at good approximation of the individual layers (endometrium-endometrium; myometrium-myometrium) of the uterine wall. Future randomized controlled trials with adequate power should be designed to evaluate this specific hypothesis using short-term surrogate outcomes, such as scar defect and remaining myometrium evaluated by ultrasound at 6–9 months postcesarean.

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TO THE EDITORS: We read with interest the article by Cardonick et al1 that compared the results of 35 children who were exposed to chemotherapy in utero with 22 nonexposed children. The percentages of abnormal results on cognitive and behavioral assessment did not differ between the 2 groups, and the results were considered reassuring. To fully understand the results, we would like to address 3 issues.

First, 1 child who was exposed to chemotherapy in utero scored significantly low on both cognitive and school measurements and high (≥98% of peers) on 4 behavioral syndrome scales. Do the authors have more information on the severity and potential organ damage, eventually supported by brain computed tomography scan or magnetic resonance imaging? Moreover, it would be of interest to know whether these problems can be accounted for by other confounding factors (for example, obstetric complications) or may be related to prenatal exposure to chemotherapy.

Second, a remarkable finding in the study of Cardonick et al1 is the high cognitive mean scores on the IQ-tests (mean Full Scale Intelligent Quotient: 111.71 for the exposed group and 112.43 for the nonexposed group) and on the Bayley Scales of Infant and Toddler Development—III (111.43 for the exposed group and 118.13 for the nonexposed group). Compared with the norm of 100 and a standard deviation of 15, which is provided by the respective tests, the mean scores reported by the authors are almost 1 standard deviation above the norm.

Third, in the current study, mean gestational age at birth did not differ between the groups with normal (54/57) and abnormal (3/57) cognitive outcome. The authors conclude that premature birth did not predict developmental outcome. An interesting question is whether this conclusion also holds position when a predictive model is applied to the data. In literature, the long-term negative impact of prematurity on cognitive development has been demonstrated repeatedly.2

We hope that these clarifications improve our insight in the long-term outcome and safety of prenatal exposure to chemotherapy.

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Development of children born to mothers with cancer during pregnancy: comparing in utero chemotherapy-exposed children with nonexposed controls

TO THE EDITORS: We read with interest the article by Cardonick et al1 that compared the results of 35 children who were exposed to chemotherapy in utero with 22 nonexposed children. The percentages of abnormal results on cognitive and behavioral assessment did not differ between the 2 groups, and the results were considered reassuring. To fully understand the results, we would like to address 3 issues.

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REPLY

Thank you Tineke Vandenbroucke, MSc and Dr Amant for your thoughtful questions. We share your passion to treat pregnant women who are diagnosed with cancer so that they are able to make informed decisions, deliver healthy infants, and maintain their health and their treatment during the pregnancy and after delivery.

The child in question was twin B of a dichorionic diamniotic twin pregnancy that was complicated by the diagnosis of ovarian cancer at 14 weeks gestation. Chemotherapy included 4 cycles of cisplatin/paclitaxel. Because of malpresentation of twin A, a primary cesarean delivery was performed at 38 weeks gestation. Twins A and B had Apgar scores of 9,9 and 8,9 and birthweights of 2608 and 2633 g. respectively. Twin B required phototherapy for jaundice but had no other medical issues that were recognized during the neonatal admission. There were no delays in language or motor skills in early childhood for either twin.

At age 5 years, the mother noted tic-like movements, difficulties in the first grade, auditory processing issues, and preoccupation with rituals in twin B. The mother believed that she herself has Asperger’s syndrome and noted similar features in this child. At age 10 years, twin B demonstrated deficits in receptive and expressive language and decreased eye contact. A computed tomography scan was reportedly normal during his evaluation according to the mother, but we did not view directly a copy of this report. Current diagnoses for twin B are Tourette’s syndrome, obsessive compulsive disorder, and Asperger’s syndrome. Twin A is without disabilities.

The cognitive mean scores (Full Scale Intelligent Quotient and Bayley Scale of Infant Development—III [BSIDIII]) for this sample do appear to be slightly above what would be found in the general population. By the current “deviation IQ” definition of IQ test standard scores, approximately two-thirds of all test-takers obtain scores from 85 to 115 and approximately 5% of the population scores above 125. Our sample scores appear to fall in line with 66% of the general population with the following distribution: BSID III cognitive scores: range = 95–145; median = 110; mode = 110; mean = 113; Full Scale Intelligent Quotient scores: range = 74–141; median = 114; mode = 96; mean = 112.

Our sample of mothers who were diagnosed with cancer (and their children) may also be representative of an “above average” socioeconomic environment based on maternal education and financial stability, thus resulting in the slightly higher mean scores. The children came from enriched and highly verbal homes. It is not an unusual profile for some very young children to score quite high because of verbal enrichment that at times evens out once school age because there is a more level playing field after formal educational exposure.

We agree with previously reported findings that issues with future developmental performance often are related to premature gestational age at birth. We also agree that iatrogenic preterm deliveries at <35-36 weeks’ gestation should be discouraged when cancer is diagnosed during pregnancy and when treatment can be offered to extend gestation. In our sample, 24 infants (18 exposed, 6 control infants) of 57 infants (42%) were delivered at <37 weeks’ gestation. The children in the chemotherapy-exposed group delivered at a statistically significant earlier gestational age, compared to the control group. However, we did not find a significant difference in mean gestational ages between the children who scored within the normal range compared with those with abnormal results in either the cognitive or behavioral areas. Only 3 children who were delivered at 32, 38.6, and 40 weeks’ gestation showed poor scores on developmental testing. Gestational ages of the 12 children with clinical behavior scores ranged in the exposure group from 32.4—39.3 weeks’ gestation and in the control group from 35.1—40.1 weeks’ gestation. Per your suggestion, an applied predictive model confirmed our initial findings that gestational age was not predictive of developmental scores for the 29 children who underwent assessment on the BSIDIII, the 28 children on the Wechsler Preschool and Primary Scale of Intelligence-R/Wechsler Intelligence Scale for Children-III, or the 14 children who completed the math and reading tests. How ever and interestingly, when scores were plotted separately for the exposed and control groups, we noted a significant relation between gestational age and cognitive scores on the BSIDIII, with a 2.3-point increase in the BSIDIII cognitive score for each gestational week gained. This was found to be true only for the exposed group (\(P = .026\)). This predictive correlation of prematurity and developmental outcome will be further studied as we continue to grow our sample size with increased subjects in both the control and chemotherapy-exposed groups.