mutations in 192 Chinese patients with primary ovarian insufficiency did not identify a mutation in *DMC1*.[4]

We suggest that mutations in genes encoding proteins that regulate meiosis can result in autosomal recessive primary ovarian insufficiency in humans, although our findings await confirmation by independent groups. However, our results are consistent with the finding that *Hfm1*-deficient mice are infertile.[5] Further investigation of *HFM1* in larger series of women with primary ovarian insufficiency and in infertile men is warranted.

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Cancer Risk among Children Born after Assisted Conception

TO THE EDITOR: Williams et al. (Nov. 7 issue)[1] reported no increase in the overall cancer risk among British children born after assisted conception. However, the study has several limitations that deserve attention because the conclusions are important to both future research and the health of children born after assisted conception.

The correctness of deterministic linkages depends on the completeness of the data and may vary according to age, with lower rates of linkage for children 1 to 9 years of age.[2] Consequently, it is possible that records were missed or misclassified, leading to an underreporting of the accuracy of the linkage. The authors found overall cancer risks that were similar to those reported in other studies, with considerable overlap in confidence intervals, but the studies they refer to have indeed found a significant excess risk. We found that the risk of early-onset acute lymphoblastic leukemia was 2.5 times as high among children born after assisted conception,[3] and the same assessment was reported in a recent meta-analysis.[4] Our study emphasizes that age at onset of cancer should be taken into consideration and that cancers with differing causes should not be lumped into one category.[5]

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TO THE EDITOR: Williams et al. report that children born after assisted conception have a risk of cancer that is similar to that of children born without such assistance. Assisted conception can be achieved with in vitro fertilization (IVF), alone or in combination with intracytoplasmic sperm injection (ICSI). Notably, couples with male-factor infertility are more likely to undergo ICSI. Infertility in a couple could be due to male-factor infertility in up to 50% of cases. The risk of birth defects appears to be higher when assisted conception with ICSI is used, but not when only IVF is used.[1]

Men with azoospermia have an increased risk of the subsequent development of cancer, which suggests that severe male-factor infertility and cancer development may share a common cause.[2] Epigenetic modifications such as DNA methylation are important regulators of both spermatogenesis[3] and carcinogenesis.[4] Had the authors evaluated whether assisted conception occurred by means of ICSI, it would have been possible to discern whether genetic abnormalities in the father could have modified the risk of childhood cancer.

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THE AUTHORS REPLY: Iliadou et al. comment on the effect missing data may have on deterministic linkage. Our linkage protocol (see Table S2 in the Supplementary Appendix of the article, available at NEJM.org) was designed to overcome this potential problem by not excluding possible matches involving missing data. A very large number of potential linkages (4,677,887) were generated with the use of this inclusive approach. Given our exacting protocol and the fact that linkage involved primarily parental information, our match rates should be independent of the child's age. We are confident that our data linkage was exhaustive in terms of attempting to identify cases of cancer.

Previous studies have shown small absolute increased risks of cancer, specifically leukemia,[1,2] in association with assisted conception. Our study showed no such increase; however, our confidence interval for the overall risk of cancer does overlap with that of an earlier, smaller, albeit population-based, study.[3] The majority of previous studies are too small to detect rare outcomes, and even the recent meta-analysis[2] cited by Iliadou et al. included significantly fewer children than our large cohort study. Furthermore, many previous studies have methodological limitations. Iliadou et al. refer to a case–control study[1] in which children hospitalized with noncancer diagnoses were used as controls. Such children may not be representative of the general population. In addition, it is difficult to estimate the effect of consent bias in such studies. Our study design, which relied on population-based registry data, avoids such biases.

Caution should indeed be exercised when cancers with different causes are grouped. However, cancer of any type, or its absence, is a key marker of long-term health. Couples considering assisted conception are likely to ask their clinician about increased cancer risk in resulting offspring but are unlikely to be overly concerned about an increased risk for one diagnostic subgroup as compared with another. Therefore, we presented data for "overall cancer risk" and data for diagnostic subgroups separately.

In response to Ramasamy et al.: we did investigate the risk of childhood cancer according to the type of assisted conception and the infertility diagnosis. We found no overall increased risk in children conceived with the use of ICSI (standardized incidence ratio [SIR], 1.07; 95% confidence interval [CI], 0.53 to 1.49) or in those conceived to couples with a diagnosis of male-factor infertility (SIR, 0.92; 95% CI, 0.70 to 1.57) (Table S4 in the Supplementary Appendix).

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Since publication of their article, the authors report no further potential conflict of interest.

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Mutant Prolactin Receptor and Familial Hyperprolactinemia

TO THE EDITOR: Newey et al. (Nov. 21 issue)[1] compare the mutant prolactin receptor with other mutant endocrine receptors (parathyroid hormone and growth hormone) characterized by loss of function (hypocalcemia and short stature, respectively). The authors attempt to explain the reproductive abnormalities in their pedigree as being the result of hyperprolactinemia and excessive signaling by the prolactin receptor. They point out the persistent postpartum galactorrhea of the proband is indicative of excess prolactin signaling. However, they report a loss of function in relation to this mutation in heterologous systems. Hyperprolactinemia in the presence of a loss-of-function mutation would not lead to increased signaling. One possibility is that the reproductive abnormalities are mediated by a second receptor, as is the case in syndromes of resistance to other hormones (thyroid hormone and glucocorticoids). Alternatively, the reproductive abnormalities seen could be due to loss of function. One way to resolve this question would be to determine the patients' clinical response to cabergoline: if oligomenorrhea and infertility were due to excess prolactin signaling, one would expect these conditions to resolve with the normalization of prolactin levels after treatment with a dopamine agonist, and if these condition were due to a loss of function in prolactin-receptor signaling, then dopamine agonist treatment would have no effect, despite the normalization of prolactin levels.

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TO THE EDITOR: Newey at al. identified a germline loss-of-function mutation affecting the prolactin receptor as a cause of familial hyperprolactinemia in three sisters, two of whom presented with oligomenorrhea and one with infertility. Aside from its essential role in lactation, prolactin has no established role in reproductive function in humans.[1] Therefore, it is unclear whether the inactivating mutation in the gene encoding the prolactin receptor (*PRLR*) explains the reproductive phenotypes in the three sisters. Newey et al. speculate that the hyperprolactinemia observed in the three sisters may have induced hypogonadism owing to the loss of hypothalamic pulsatile secretion of the gonadotropin-releasing hormone. However, this explanation does not seem logical to me because inhibition of the secretion of the gonadotropin-releasing hormone by means of increased circulating levels of prolactin presumes the presence of a functioning prolactin receptor.[2] Therefore, an alternative explanation may be that the increased prolactin levels in the sisters represent merely a compensation for reduced signaling by the prolactin receptor and that the reproductive abnormalities are coincidental.

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No potential conflict of interest relevant to this letter was reported.

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