# Omega-3 Intake Improves Clinical Pregnancy Rate in Polycystic Ovary Syndrome Patients: A Double-Blind, Randomized Study

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**ABSTRACT** **Background:** Omega-3 fatty acids promote fertility in males and females and constitute an important factor in the normal development of the fetus.

**Objectives:** We investigated the effect of omega-3 supplements during ovulation induction treatment in women with polycystic ovary syndrome (PCOS)-related infertility.

**Methods:** A randomized, double-blind study was conducted for 60 treatment cycles in 34 women with PCOS-related oligo/anovulation referred to the fertility clinic at the Bikur Cholim/Shaare Zedek Medical Center in Jerusalem, who underwent ovulation induction with clomiphene citrate (50 mg). Seventeen women (mean age 33.9 ± 0.9 years) received omega-3 supplements (3 × 600 mg/day) and 17 received placebo capsules (mean age 32.7 ± 0.9 years) for a maximum of two cycles. We recorded their characteristics and data from their serial hormonal blood tests and ultrasound examinations. We also conducted both univariate and multivariate analyses. The primary endpoint was conception.

**Results:** There were clinical pregnancies in 8/30 (26.7%) treatment cycles for women receiving omega-3 supplements versus 4/30 (13.3%) cycles with placebo. Among overweight/obese women (body mass index [BMI] 25–35), there were clinical pregnancies in 8/27 cycles (29.6%) versus 1/19 (5.3%) with placebo ($P < 0.04$). For overweight/obese PCOS women, omega-3, lower BMI rates, and higher values of the endometrium's thickness increased the odds of becoming pregnant. No harmful side effects from the omega-3 treatment were reported.

**Conclusions:** Omega-3 supplements demonstrated beneficial effects for fertility in women diagnosed with PCOS. Among the overweight/obese participants, the increased clinical pregnancy rate was significant.

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**KEY WORDS:** clinical pregnancy, infertility, obese women, omega-3, polycystic ovary syndrome (PCOS)

Animal and human studies suggest that a diet rich in omega-3 polyunsaturated fatty acids (ω3-PUFA) has a positive impact on fertility, which affects oocyte quality, embryo implantation [1], and menstrual cycle function [2]. Cows that received omega-3 supplements had more and larger follicles with better functionality and were more fertile than those that did not receive this supplement [3,4]. In North American women, omega-3 fatty acid intake has been associated with higher fecundability [5].

Since about 15% of couples of reproductive age around the world present with infertility [6], it is important to identify potentially modifiable risk factors, such as diet, that impact both natural fecundability and assisted reproductive outcomes [7].

Polycystic ovary syndrome (PCOS) is a multifactorial, complex genetic, endocrine, and metabolic disorder characterized by chronic anovulation, polycystic ovaries, and hyperandrogenism [8]. An estimated 4% to 8% of women exhibit PCOS worldwide [9], and a subset of these patients are resistant to fertility treatment and fail to conceive despite ovulation induction treatment [10]. Studies have shown that women with PCOS have smaller oocytes versus controls, similar to what is seen in diabetic, insulin-resistant women [11], and also in obese women [12]. This condition is known to adversely affect fertility outcomes [12]. Studies evaluating the effects of omega-3 on the metabolic status and biochemical characteristics of women with PCOS [13,14] found beneficial results in their insulin metabolism, serum triglycerides, and very-low-density lipoprotein cholesterol [13,14] as well as improved androgenic profiles [14]. An 8-week course of omega-3 supplements had beneficial effects on their luteinizing hormone (LH), LH/ follicle-stimulating hormone (FSH), and adiponectin [13]. However, to the best of our knowledge, no study has shown the effect of omega-3 on PCOS clinical pregnancy rates.

The objective of this study was to evaluate the effect of omega-3 supplementation on infertile women presenting with PCOS, including overweight or obese women, during ovulation induction using clomiphene citrate.

## PATIENTS AND METHODS

### PARTICIPANTS AND OMEGA-3 ADMINISTRATION

This study was a prospective, randomized, double-blind, placebo-controlled clinical trial conducted from December 2012 to January 2014 among PCOS women referred to the fertility clinic at the Bikur Cholim/Shaare Zedek Medical Center in Jerusalem, who were showing chronic oligo/anovulation due to PCOS, classified as group II by the World Health Organization (WHO) [15]. Women aged 25–38 who had been unable to conceive for 12–30 months and were undergoing ovulation induction with 50 mg of clomiphene citrate for 5 days were included in the study. Patients who used anticoagulant medications were excluded from the study.

Forty-two women who were suitable at the time of the study and agreed to participate were screened and double-blind randomized into two groups. We recruited 34 for the clinical trial; 4 were lost to follow-up, and 4 subsequently declined to participate. The study group received omega-3 fatty acids, and the control group received a placebo. All patients were treated with the same routine ovulation induction regimen.

The appearance and packaging of the omega-3 and placebo capsules was similar. Each package had a number label assigned by a staff member at the SUPHERB company (Netanya, Israel). There was no order, regularity, or periodicity in the distribution of the numbers, which were haphazardly assigned and evenly divided between the two groups. The researchers and the clinical staff had no access to the randomization coding or any knowledge regarding the assignment of individual participants to the two groups. Also, the SUPHERB staff member who assigned the package numbers had no information about the clinical details or patient outcomes until the end of the study.

### TREATMENT REGIMEN

Weight, height, body-mass index (BMI kg/m$^2$), and basal hormone levels were measured before study initiation. Following basal hormone evaluation, all women received 50 mg of clomiphene citrate for 5 days starting on day 12 of the cycle, and were followed up with blood hormone testing and ultrasounds for ovulatory response [Table 1]. In addition to the standard treatment protocol for ovulation induction, patients randomized to the study group received 3 × 600 mg capsules of Omega Max-3 (SUPHERB) per day, each capsule containing 360 mg EPA and240 mg DHA (a total of 1800 mg fish oil a day), and those randomized to the control group received three placebo capsules containing sunflower oil each day. The omega-3 and the placebo were first started with the onset of their menses. Both groups took the capsules daily throughout the entire time until the women either conceived or completed two clomiphene cycles. The omega dose was within the range of the recommended level for the management of specific health conditions [16,17], and the length of our study was based on findings that

**Table 1.** Characteristics and clinical data with their outcomes

| | Omega | Placebo | *P*-value |
|---|---|---|---|
| Patients | 17 | 17 | |
| Cycles | 30 | 30 | |
| Age (years) | 33.9 ± 0.9 | 32.7 ± 0.9 | 0.35 |
| Body mass index (kg/m2) | 30.67 ± 2.09 | 27.27 ± 1.86 | 0.02 |
| Smokers | 7.1% | 7.7% | 0.70 |
| Type of infertility, primary | 29.4% | 17.6% | 0.43 |
| Duration of infertility (years) | 1.2 ± 0.1 | 1.2 ± 0.0 | 0.55 |
| FSH (IU/L) | 7.0 ± 0.4 | 7.1 ± 0.4 | 0.80 |
| LH (IU/L) | 7.6 ± 0.6 | 7.8 ± 0.8 | 0.77 |
| Total testosterone (nmol/L) | 1.5 ± 0.1 | 1.3 ± 0.2 | 0.51 |
| Free androgen index | 4.5 ± 0.5 | 3.8 ± 0.4 | 0.30 |
| Androstenedione (nmol/L) | 5.3 ± 0.7 | 3.6 ± 0.7 | 0.12 |
| Estradiol (pmol/L), both cycles | | | |
| Basal | 120.1 ± 11.6 | 178.4 ± 13.9 | 0.03 |
| Preovulatory peak | 1503.15 ± 121.9 | 1545.55 ± 225.7 | 0.79 |
| Basal, BMI 25–35 | 120 ± 6.1 | 175 ± 7.8 | 0.06 |
| Preovulatory peak, BMI 25–35 | 1458 ± 23.2 | 1550.07 ± 35.8 | 0.8 |
| Progesterone (nmol/L), both cycles | | | |
| Preovulatory peak | 2.2 | 2.0 | 0.9 |
| Midluteal | 61.8 ± 4.2 | 66.02 ± 3.7 | 0.46 |
| Preovulatory peak, BMI 25–35 | 2.08 | 2.0 | 0.9 |
| Midluteal, BMI 25–35 | 55.4 ± 2.6 | 61.6 ± 3.8 | 0.3 |
| Endometrium (mm), both cycles | | | |
| Basal | 5.5 ± 0.3 | 5.1 ± 0.4 | 0.38 |
| Preovulatory peak | 9.1 ± 1.1 | 9.3 ± 1.6 | 0.72 |
| Basal, BMI 25–35 | 5.6 ± 0.9 | 2.57 ± 1.6 | 0.1 |
| Preovulatory peak, BMI 25–35 | 8.65 ± 0.8 | 8.37 ± 0.6 | 0.4 |
| Lead follicles ( > 16 mm), both cycles | 1.6 ± 0.18 | 1.2 ± 0.15 | 0.15 |

Values are expressed as mean ± SE or percentage
$P < 0.05$, statistically significant

In the omega-3 group and in placebo group: first treatment cycle n=17, second treatment cycle n=13.
BMI 25–35: First treatment cycle in omega-3 group n=15
In the placebo group n =11, Second treatment cycle in omega-3 group n=12 and in placebo group n =8

BMI = body mass index (km/m$^2$), FSH = follicle-stimulating hormone, LH = luteinizing hormone

**Table 2.** Patients and cycles showing clinical pregnancy outcomes

| | | Omega | Placebo | *P*-value |
|---|---|---|---|---|
| All patients | First treatment cycle | 2/17 (11.8%) | 1/17 (5.9%) | 0.50 |
| | Second treatment cycle | 6/13 (46.2%) | 3/13 (23%) | 0.20 |
| | Both cycles, patients | 8/17 (47.1%) | 4/17 (23.5%) | 0.15 |
| | Per cycle | 8/30 (26.7%) | 4/30 (13.3%) | 0.30 |
| | Within two cycles | 8/15 (53.3%) | 4/14 (28.6%) | 0.1 |
| | Twin pregnancy | 1/17 (5.8%) | 1/17 (5.8%) | 0.60 |
| BMI 25–35 km/m$^2$ | First treatment cycle | 2/15 (13.3%) | 0/11 (0%) | 0.50 |
| | Second treatment cycle | 6/12 (50%) | 1/8 (12.5%) | 0.08 |
| | Both cycles, patients | 8/15 (53.3%) | 1/11 (9.1%) | 0.02 |
| | Within two cycles | 8/14 (57.14%) | 1/8 (12.5%) | 0.04 |

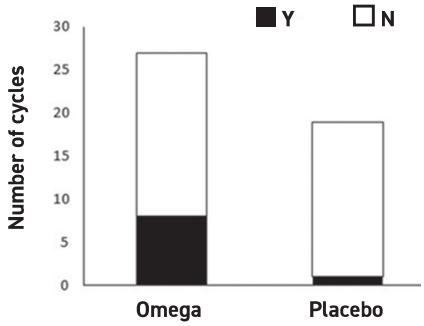
Values are expressed as mean ± SE or percentages
*P* < 0.05, statistically significant

In omega-3 group and in placebo group: first treatment cycle, n =17, second treatment cycle, n =13
In the BMI 25–35 km/m$^2$ omega-3 group, first treatment cycle, n =15, second treatment cycle, n =12
In the placebo group in first treatment cycle, n=11 and second treatment cycle, n=8.

Within two cycles, all women who conceived during the first cycle or completed both cycles were considered

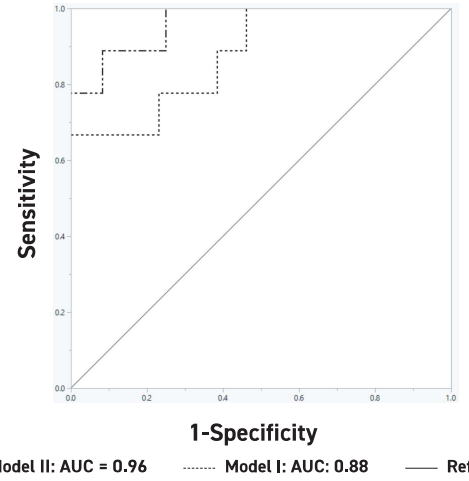
**Figure 1.** The number of clinical pregnancies per treatment cycles within a BMI range of (25–35) in the omega group and in the placebo group in PCOS patients
BMI = body mass index, N = no pregnancy. Y = pregnancy

**[A]** Omega group (29.6%, 8/27) versus placebo group (5.3%, 1/19), (*P* < 0.04)




**[B]** ROC curve for multivariate models illustrates the incremental value of an additional parameter (namely the thickness of the endometrium) in Model II on the quality of the model; i.e., the area under the curve increased from 0.88 to 0.96

Model I includes two predictors of clinical pregnancy: group (omega-3/placebo) and body mass index (BMI). Model II includes three predictors: group (omega-3/placebo), BMI, and endometrial thickness




the effects of omega-3 can be observed after 2 or 3 months [18]. All participants were followed monthly and data for size and quantity of follicles, estradiol (E2) (pMol) and progesterone (P) levels (nMol) in the blood, and thickness of the endometrium at ovulation were recorded. Clinical pregnancy was determined by visualization of a fetal heartbeat at gestational week 7–8 weeks via a transvaginal ultrasound.

### HORMONAL AND FOLLICULAR MEASUREMENTS

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, free androgen index (FAI), and androstenedione levels were assessed within a maximum of 2 weeks before study initiation (baseline). Follicular and endometrial development were assessed with serial transvaginal ultrasonography (6.5 MHz probe; Elscint, Herzliya, Israel). Measurements included the mean diameter of the follicle (two dimensions) and the full endometrial thickness (maximal midsagittal plane). The lead follicles (≥ 16 mm) were carefully recorded. Ovulation was validated by midluteal serum P levels monitored 7–9 days after hCG or triptorelin administration. Blood samples for intracycle hormone measurement were drawn on the same days as the follicular measurements were performed. Serum E2, P, FSH, and LH levels were measured using Chemiluminescent Microparticle Immunoassay (CMIA, Abbott Diagnostics, Abbott Park, IL, USA). Other hormones were measured using the radioimmunoassay (RIA) method (Diagnostic Products, Los Angeles, CA, USA).

### STATISTICAL ANALYSIS

Data were analyzed and reported only for patients who completed at least one treatment cycle. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Descriptive statistics included frequency, central tendency (mean), and dispersion (frequency, range). The chi-square test or Fisher's exact test were used to compare categorical variables between

groups. The student *t*-test was used for variables that were distributed normally, while the Mann-Whitney test was performed for variables that had no normal distribution. Two-tailed *P*-values < 0.05 were considered significant. Multivariate binary logistic regression was performed, and odds ratios and receiver operator characteristic (ROC) curves were calculated using JMP pro15 software (SAS Institute Inc., Cary, NC, USA).

## RESULTS

A total of 34 patients who completed 60 ovulatory cycles met inclusion criteria and were randomized and included in the study. Their characteristics are summarized in Table 1. The two randomized groups of 17 patients each were comparable in terms of age and smoking history, type and duration of infertility, and baseline preovulatory hormone levels. The mean BMI in the study group, 30.67 ± 2.09, was significantly higher than the mean BMI of 27.26 ± 1.96 in the placebo group ($P = 0.02$). The basal estradiol level in the placebo group, 178.4 ± 13.9 pmol/L, was significantly higher than the mean, 120.1 ± 11.6 pmol/L, in the omega-3 group ($P = 0.03$). There was no significant difference in preovulatory hormone levels and in the peak endometrium mean level between the omega and placebo groups [Table 1].

The number of leading follicles that developed in women from the omega-3 group was not significantly higher than in the placebo group. In the total of 30 cycles completed by the women in each of the two groups, there were eight pregnancies (26.7%) among the women who took the omega-3 versus four pregnancies (13.3%) among those who took the placebo ($P < 0.3$) [Table 2]. Within two cycles, there were eight pregnancies (53.3%) among the women who took the omega-3 versus four (28.6%) among those who took the placebo $P < 0.17$) [Table 2].

Since there was a significant difference in BMI between the omega-3 group and the placebo group, we specifically looked at the rate of clinical pregnancies among the patients who were overweight or obese (BMI 25–35), who constituted the majority, namely, 15/17 women in the study group and 11/17 in the placebo group. In the omega group, one patient was morbidly obese (BMI 42) and one patient was normal (BMI 22). In the placebo group, one patient was severely obese (BMI 37) and five patients were normal (BMI 23–24). Among the women who were overweight or obese, there was a significantly higher pregnancy rate in the omega group, with clinical pregnancies in 8/27 cycles (29.6%) versus 1/19 cycles (5.3%) among those who took the placebo ($P < 0.04$) [Table 2, Figure 1A].

There was no significant difference in preovulatory hormone levels and in the peak endometrium mean level between the two groups of overweight/obese women [Table 1].

A multivariate logistic regression was performed for all women who were overweight or obese (BMI 25–35) and who conceived on the first cycle or completed both cycles. A total of 22 women met these criteria, including 14 in the omega-3 group and eight in the placebo group. The model included the dependent variable pregnancy at the end of the experiment as a binary parameter Yes/No. The independent variables were group (omega-3/placebo) and BMI (Model I). The model was highly significant ($P = 0.006$), with *P*-values of 0.003 and 0.016 for group and BMI effects, respectively, and an area under the curve (AUC) = 0.88 (95% confidence interval [95%CI] 0.58–0.97) [Table 3, Figure 1B]. This means that for two women with the same BMI, the odds of becoming pregnant when taking omega-3 were 1.84-fold at 95%CI, which was 65-fold higher than the placebo ($P = 0.022$). For all the women, regardless of whether they received omega-3 or the placebo, the odds of becoming pregnant increased by 1.76-fold for each one-unit decrease in BMI, with borderline significance in the sample ($P = 0.053$).

A univariate analysis was performed with all variables to test whether there were significant differences between those who conceived and those who did not. The only variable that was significant ($P = 0.028$) was endometrial thickness, an important factor regarding conception, and therefore it was added as a third independent variable (Model II). After excluding one patient with an outlier endometrial thickness that was 2.9 standard deviations above the average, the model was highly significant ($P = 0.0001$), with *P*-values of 0.0002, 0.0008, and 0.0010 for the study vs. the control group, BMI, and endometrial thickness, respectively, and an AUC = 0.96 (95%CI 0.73–1.00) [Figure 1B]. Thus, in our study, taking omega-3 supplements increased the odds of becoming pregnant. Increases in BMI reduced the odds of achieving pregnancy, while increases in endometrial thickness increased the odds. The odds ratio values in this model were very inflated due to its small sample size and are not presented here.

**Table 3.** Odds ratios of becoming pregnant including 95% confidence interval and *P*-values for multivariate logistic regression models

| | Odds ratio (95% confidence interval) | *P* value | Area under the curve (95% confidence interval) |
|---|---|---|---|
| Multivariate model 1 | | 0.005 | 0.88 (0.58–0.97) |
| Group: Omega / Placebo | 65.17 (1.84–2308) | 0.022 | |
| Body mass index | 0.57 (0.32–1.01) | 0.053 | |

Tests and confidence intervals on odds ratios are Wald-based

Area under the curve confidence interval was obtained using Bootstrap procedure

For two women with the same body mass index (BMI), the odds of becoming pregnant when taking omega was 65-fold higher than the placebo with a *P*-value of 0.022. Regarding BMI, the odds of becoming pregnant regardless of what treatment she took increases by 1.76 (the reciprocal value, 1/0.57=1.76) fold for each decrease in BMI by one unit. The *P*-value 0.053 is on the border of significance. Area under the curve, a measure of the quality of the model, was 0.88

Patients in this study did not experience harmful side effects from the omega-3 treatment.

## DISCUSSION

To the best of our knowledge, this study is the first randomized, double-blind, controlled trial investigating the effects of omega-3 on PCOS fertility. We showed that the overweight or obese participants who received the omega-3 supplements achieved a significantly higher rate of clinical pregnancy compared to the overweight or obese participants who received the placebo. In addition, the entire omega-3 group achieved a higher number of clinical pregnancies than the entire placebo group; however, the numbers were not significant).

Legro et al. [19] studied clinical pregnancies in overweight/obese PCOS women after four treatment cycles with clomiphene. They reported that 6/47 (12.8%), 12/48 (25%), and 13/47 (27.7%) women were pregnant after preconception treatment with continuous oral contraceptives, lifestyle modification (including caloric restriction, anti-obesity medication, behavioral modification, and exercise), or the combination of both, respectively. In addition, after four immediate clomiphene treatment cycles (with no BMI restrictions), 25/187 (13.4%) women with PCOS achieved clinical pregnancies. In contrast, in our study, there were pregnancies in 8/27 (26.7%) women with PCOS who were treated with clomiphene and randomized to receive supplemental omega-3 after only two treatment cycles. Thus, in our study, omega-3 increased the rate of clinical pregnancy while reducing the number of treatment cycles.

It has been demonstrated that obesity has a negative influence on fertility [20]. It has also been shown that women with PCOS, who in their first IVF/ICSI treatment cycles were obese, had lower cumulative clinical pregnancy rates compared with women of normal weight and compared with women who were obese but did not have PCOS [21]. Our high rate of clinical pregnancies was achieved despite the fact that 15/17 women (88.2%) who received the omega-3 were overweight or obese (BMI 25–35).

It was found that, for every unit of increase in BMI, there is an estimated 5% decrease in the odds of conception [22]. This result was also seen in our study, where we found that the odds of becoming pregnant decreased by 43% for each increase of one unit of BMI. However, this figure is most probably inflated due to our small sample size and statistical power. Further study using a larger sample is needed.

While an increase in BMI negatively affected the odds of becoming pregnant, an increase in the endometrial thickness increased the odds. Endometrial thickness is an important factor in the ability to conceive and is regarded as a prognostic factor in IVF/ICSI treatment [23]. Ovulation induction with clomiphene might result in lower endometrial thickness compared with other ovulation induction regimens [24]. In our study, we did not find a significant lowering of endometrial thickness between the groups. However, we did find that for two women with the same endometrial thickness, the odds of becoming pregnant when taking omega-3 were higher than the placebo.

PCOS patients taking omega-3 have shown improvement in numerous risk factors for pregnancy, including an anti-obesity effect and glycemic and hormonal homeostasis [25]. Perhaps omega-3 intake improved several of the parameters that PCOS patients, and especially overweight/obese PCOS patients, present with, which may have contributed to improvement in their clinical pregnancy rate. In this study, there was a significant difference between the basal E2 levels of the groups, but this did not result in differences in other hormone levels.

The randomized, double-blind, controlled trial design of this study was a strength. All participants met the consensus criteria for PCOS and underwent the same treatment for ovulation induction. The entire omega-3 group received the same dose of omega-3. However, because our study was double-blind and randomized, we considered randomness in the patients' food intake, and we did not exclude patients based on their diet. We believe that the primary limitation of this study is the small number of participants and the relatively short duration of the study.

## CONCLUSIONS

Omega-3 treatment versus placebo significantly improved the clinical pregnancy rate in overweight/obese women with PCOS. For overweight/obese PCOS women, omega-3 supplementation, lower BMI rates, and higher values of the endometrium thickness increased the odds of becoming pregnant.

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**Capsule**

## Multisystem inflammatory syndrome in children

Multisystem inflammatory syndrome in children (MIS-C) is a severe complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that affects one in 10,000 infected children, is reminiscent of Kawasaki disease, and its etiology remains unknown. **Lee** et al. performed whole-exome and whole-genome sequencing on a cohort of MIS-C patients and uncovered autosomal-recessive deficiencies of OAS1, OAS2, or RNase L in around 1% of the cohort (see the Perspective by Brodin). These genes are components of a signaling pathway that suppresses inflammation in double-stranded RNA-stimulated mononuclear phagocytes. Thus, single-gene recessive inborn errors of the OAS–RNase L pathway can result in uncontrolled inflammatory cytokine production by mononuclear phagocytes after SARS-CoV-2 infection, potentially explaining the origins of MIS-C in some children.

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**Capsule**

## How lymphomas outcompete

Lymphomas are cancers of the immune system that arise from B cells undergoing a strict natural selection process required for immunity. These highly mutating and dividing B cells vigorously compete against each other for T cell help to survive. Mutations affecting *B cell translocation gene 1* (*BTG1*) are exclusive to B cell lymphoma and associated with poor clinical outcomes. **Mlynarczyk** and colleagues found that mutant *BTG1* effects were limited to conferring B cells with only subtle acceleration of their T cell help response. This effect occurred at the checkpoint that governs natural selection of B cells, so these cells became supercompetitors that outpaced and replaced their normal counterparts. This behavior mirrors embryonic-specific supercompetition processes, pointing to BTG1 as an evolutionary gatekeeper of natural selection during the adaptive immune response.

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