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Benign Breast Disorders in Levonorgestrel-releasing Intrauterine Device Users: Evidence from a Prospective Cohort Study

Levonorgestrel Salınımlı Rahim İçi Araç Kullanımında Benign Meme Bozuklukları: Prospektif Kohort Çalışması

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Abstract

Objective: This study aimed to evaluate the incidence of benign breast disorders in women using levonorgestrel-releasing intrauterine devices (LNG-IUD) and to assess the relationship between duration of use and these outcomes.

Methods: A prospective observational cohort study was conducted at a tertiary care center. The study included premenopausal women aged 18 years or older who had used an LNG-IUD for at least 12 months. Breast imaging was performed using standard ultrasonography. Lesions were classified according to the breast imaging reporting and data system. The primary outcome was the presence of benign breast diseases, including simple cysts, fibroadenomas, and fibrocystic changes.

Results: Eighty women with a mean age of 47.2±4.4 years and a mean body mass index (BMI) of 28.1±3.9 kg/m^2 were included in the study. Benign breast abnormalities were found in 57 women (71.2%); among these, the majority (61.3%) were simple cysts, followed by fibrocystic changes (15.0%) and fibroadenomas (1.3%). Women with benign outcomes had lower baseline hemoglobin levels than those without benign outcomes (12.4 vs. 13.1 g/dL, p=0.018). No significant differences were observed in age, BMI, or number of births. In multivariate logistic regression, LNG-IUD duration was not significantly associated with benign outcomes (adjusted odds ratio=0.44, 95% confidence interval: 0.12-1.57).

Conclusion: Benign breast complications are common among women using LNG-IUDs and are not affected by duration of device use. These findings support the safety profile of LNG-IUDs with respect to benign breast health and may help clinicians provide reassurance during contraceptive counseling.

Keywords: Levonorgestrel-releasing intrauterine device (LNG-IUD), Mirena®, benign breast disorders, breast cysts, fibrocystic breast disease

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Öz

Amaç: Bu çalışmanın amacı, levonorgestrel salan rahim içi araç (LNG-IUD) kullanan kadınlarda benign meme hastalıklarının insidansını değerlendirmek ve cihaz kullanım süresi ile klinik sonuçlar arasındaki ilişkiyi incelemektir.

Yöntem: Bu prospektif, gözlemsel kohort çalışması üçüncü basamak bir sağlık merkezinde yürütülmüştür. Çalışmaya, en az 12 aydır LNG-IUD kullanan, 18 yaş ve üzeri premenopozal kadınlar dahil edilmiştir. Meme görüntülemesi standart ultrasonografi yöntemiyle gerçekleştirilmiş ve saptanan lezyonlar meme görüntüleme raporlama ve veri sistemine göre sınıflandırılmıştır. Birincil sonlanım noktası, basit kistler, fibroadenomlar ve fibrokistik değişiklikleri içeren benign meme hastalıklarının varlığı olarak belirlenmiştir.

Bulgular: Çalışmaya ortalama yaşı 47,2±4,4 yıl ve ortalama vücut kitle indeksi (VKİ) 28,1±3,9 kg/m^2 olan toplam 80 kadın dahil edilmiştir. Katılımcıların 57'sinde (%71,2) benign meme bulguları saptanmıştır. Bu bulguların çoğunu basit kistler (%61,3) oluştururken, bunu fibrokistik değişiklikler (%15,0) ve fibroadenomlar (%1,3) izlemiştir. Benign meme bulguları saptanan kadınlarda başlangıç hemoglobin düzeylerinin, benign bulgusu olmayanlara kıyasla daha düşük olduğu görülmüştür (12,4'e karşı 13,1 g/dL; p=0,018). Yaş, VKİ ve doğum sayısı açısından gruplar arasında anlamlı fark saptanmamıştır. Çok değişkenli lojistik regresyon analizinde, LNG-IUD kullanım süresi ile benign meme bulguları arasında anlamlı bir ilişki bulunmamıştır (düzeltilmiş olasılık oranı=0,44; %95 güven aralığı: 0,12-1,57).

Sonuç: LNG-IUD kullanan kadınlarda benign meme bulguları sık görülmekte olup bu durum cihazın kullanım süresinden etkilenmemektedir. Bu bulgular, LNG-IUD'lerin benign meme sağlığı açısından güvenli profilini desteklemekte ve kontraseptif danışmanlık sırasında klinisyenlerin hastalara güven verici bilgi sunmasına katkı sağlayabilir.

Anahtar Kelimeler: Levonorgestrel salan rahim içi araç (LNG-IUD), Mirena®, benign meme hastalıkları, meme kistleri, fibrokistik meme hastalığı

Introduction

Levonorgestrel-releasing intrauterine devices [LNG-IUD, (Mirena®)] are one of the effective, long-acting, reversible contraceptive methods widely preferred not only for pregnancy prevention but also for the management of non-contraceptive indications such as excessive menstrual bleeding, endometrial hyperplasia, and dysmenorrhea[1]. Alongside increasing clinical use, the safety profile of LNG-IUDs has been extensively evaluated, particularly with respect to reproductive health outcomes. However, potential breast-related effects, common in women approaching perimenopause, remain an important area for discussion in clinical counseling.

Most current literature focuses on the possible association between LNG-IUD use and breast cancer risk. A large-scale Danish group study revealed a small rise in the rate of breast cancer in females utilising modern hormonal contraceptives, including LNG-IUDs[2]. Also, Yi et al.[3] similarly reported a slight increase in breast cancer risk in a nationally conducted Asian cohort study. However, there is no complete consensus on these findings in the literature, with systematic reviews and meta-analyses providing different results. While some studies suggest a low-level increase in risk, others have found no significant link between using an LNG-IUD and developing breast cancer[4,5]. In accordance with the current evidence, it should be noted that the absolute increase in malignancy risk is minimal, and this risk should be considered alongside the high contraceptive efficacy and substantial non-contraceptive clinical benefits of the LNG-IUD (American College of Obstetricians and Gynecologists)[6].

In contrast, the relationship between LNG-IUD use and benign breast diseases has received relatively limited attention in the literature. However, this concern, frequently encountered in clinical practice, leads to significant uncertainties in patient counseling and is not adequately represented in research focusing on contraceptive safety. Benign breast lesions such as simple cysts, fibrocystic changes, and fibroadenomas are commonly found in both premenopausal and perimenopausal women[7]. Although these lesions generally show a low risk of malignancy, their detection often increases patient anxiety, necessitates additional imaging, and complicates the contraceptive counseling process. Furthermore, benign breast diseases are not a homogeneous group; non-proliferative lesions are generally considered to have a minimal or negligible risk of subsequent breast cancer, while atypical proliferative lesions are known to indicate a significant increase in long-term breast cancer risk[8,9].

The biological significance of hormonal effects on benign breast pathologies also requires further investigation. Depending on dose, receptor expression, and systemic exposure levels, progesterone and synthetic progestins have been shown to modulate breast epithelial proliferation and stromal structure[10,11]. The local effect of LNG-IUDs with lower systemic hormone levels compared to oral or injectable hormonal contraceptives suggests that their potential effects

on benign breast outcomes may differ; however, evidence supporting this hypothesis is still limited[12].

This study aimed to prospectively evaluate benign breast findings in patients using LNG-IUDs, drawing on existing literature and employing standardized imaging protocols. Although the study did not include pre-treatment breast assessments and a control group not using LNG-IUDs, the research aimed to provide clinically significant prevalence data, to investigate possible associations between duration of LNG-IUD use and benign breast findings, and to lay the groundwork for more evidence-based contraceptive counseling.

Materials and Methods

Study Design, Setting, and Ethical Considerations

This prospective observational cohort study was conducted at the Obstetrics and Gynecology Department of University of Health Sciences Türkiye, Kayseri City Hospital. University of Health Sciences Türkiye, Kayseri City Hospital is a tertiary referral center serving a large urban and semi-urban population, providing routine contraceptive counseling, intrauterine device insertion, and long-term follow-up services.

The study protocol was approved by the University of Health Sciences Türkiye, Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee (approval no: 492, date: 08.07.2025). Prior to involvement in the study, written informed consent was obtained from all participants. All participants provided written consent for the use of anonymized data in scientific publications. The research was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Participants

Inclusion criteria for the study were premenopausal women aged 18 years or older who had been using a LNG-IUD; (Bayer Healthcare, Germany) continuously for at least 12 months. The LNG-IUD was implanted either for contraception or for benign gynecological indications such as excessive menstrual bleeding, dysmenorrhea, or endometrial protection during hormone therapy. Individuals with a prior diagnosis of breast or gynecological malignancy, a history of breast surgery that could affect the interpretation of breast imaging, or a known hereditary predisposition to breast cancer, including BRCA1/2 mutations, were excluded. Additionally, women with incomplete medical records or who refused to undergo breast imaging were excluded. Eligible participants were identified through the hospital's electronic contraceptive registry system and verified during gynecology outpatient visits.

Sample size calculations were performed using G*Power software (version 3.1.9.7; Heinrich Heine University, Düsseldorf, Germany) to ensure sufficient statistical power. The analysis assumed a moderate effect size (Cohen's d =0.5), a 5% significance level (α=0.05), and 80% statistical power. Based on this calculation, a minimum of 64 participants (32 per group) were needed. To account for potential missing data and loss to follow-up, the target sample size was set at 80 women.

Data Collection

Data were obtained from the hospital's electronic health record system and supplemented by structured clinical interviews during follow-up. Demographic variables included age at the time of LNG-IUD placement, parity, marital status, and education level. Clinical features included indication for LNG-IUD use, duration of device retention in the uterus, other medical conditions, and relevant gynecological history. Reproductive history, including age at menarche, menstrual cycle characteristics, and obstetric outcomes, was recorded in detail because these variables are known to be related to breast health and hormonal exposure.

Anthropometric measurements were obtained at the baseline visit as part of a routine gynecological evaluation. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters, in accordance with the World Health Organization definitions[13]. Height and weight measurements were performed by trained nurses using calibrated devices to minimize inter-observer variability.

Basic laboratory data included hemoglobin and hematocrit levels measured in routine clinical practice before or within one month after LNG-IUD placement. These parameters were included in the assessment because of their potential association with both gynecological conditions that lead to LNG-IUD placement (e.g., menorrhagia) and overall health status.

Lifestyle variables-such as family history of breast cancer and gynecological malignancies, and smoking-were systematically documented during patient interviews. To improve data accuracy and reduce recall bias, the collected information was cross-checked with electronic hospital

records. When missing or unclear data were identified, participants were contacted directly by telephone to verify the information. All data were anonymized after the collection process, and to protect confidentiality, analyses were performed only on the anonymized dataset.

Breast Imaging Assessment

All participants underwent bilateral breast ultrasonography as part of the clinical evaluation process. Imaging procedures in the radiology department were performed by board-certified radiologists with at least ten years of experience in breast imaging. High-frequency (10-14 MHz) linear-array transducers were used during the examinations, and standardized scanning protocols were followed to ensure systematic evaluation of all breast quadrants and the retroareolar region. To minimize observer bias, radiologists were not informed of the participants' contraceptive history or the clinical outcomes of the study.

In women aged 40 years and older, when breast tissue was assessed as dense or when ultrasonographic findings were unclear, additional mammographic evaluation was performed using full-field digital mammography systems. In cases where ultrasonography or mammography findings did not provide a definitive diagnosis, contrast-enhanced breast magnetic resonance imaging was performed in accordance with the diagnostic guidelines published by the American College of Radiology (ACR)[14]. This multimodal imaging approach aimed to provide a more comprehensive evaluation of lesions and to increase diagnostic accuracy.

All detected breast lesions were classified using the breast imaging reporting and data system (BI-RADS; 2013) criteria defined by the ACR. Simple cysts and typical fibrocystic changes were assigned to BI-RADS category 2 (benign), whereas fibroadenomas were assigned to BI-RADS category 2 or 3, depending on imaging characteristics. Lesions classified as BI-RADS category 3 were followed for six months to confirm stability, and cases that remained stability were considered benign. Cases requiring biopsy and those with atypical hyperplasia or malignancy detected on histopathological examination were excluded from the benign lesion group.

Imaging reports and raw images were reviewed by two senior radiologists during consensus meetings to ensure accurate and reproducible lesion classification. Inter-observer agreement was monitored by randomly selecting 15% of cases and evaluating them using the double-reading method, resolving any discrepancies through consensus. This quality control process was implemented to increase the reliability of imaging assessments and minimize classification errors.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean and standard deviation or median and interquartile range. Categorical variables were expressed as frequencies and percentages. Normality of the data was assessed using the Kolmogorov-Smirnov test and visual inspection. To assess demographic and clinical differences between women with and without benign breast disease, the independent samples t-test was used for normally distributed continuous variables and the Mann-Whitney U test was used for non-normally distributed continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test. A two-sided p-value of <0.05 was considered statistically significant. A multivariate logistic regression model was used to evaluate the independent predictors of benign breast disease. Model fit was assessed using the Hosmer-Lemeshow test. Missing data were addressed using complete-case analysis, and LNG-IUD duration was divided into quartiles for sensitivity analyses.

Results

A total of 80 premenopausal women who had used an LNG-IUD for at least 12 months were included in the analysis. The mean age of participants was 47.2±4.4 years, and the mean BMI was 28.1±3.9 kg/m^2. The majority of women (71.2%) had at least one benign breast disorder detected on imaging. Baseline characteristics are presented in Table 1. A flow diagram of patient recruitment and analytic sample selection is provided in Supplementary Figure 1.

Among the 57 women with benign outcomes, 61.3% had simple cysts, 15.0% had fibrocystic changes, and 1.3% had fibroadenomas. Multiple lesions were detected in 22 women (27.5%), and bilateral lesions were present in 18 women (22.5%) (Table 2).

When women with and without benign breast disorders were compared, no significant differences were observed in mean age, BMI, or parity. However, baseline hemoglobin levels were significantly lower among women with benign outcomes (12.4 g/dL vs. 13.1 g/dL, p=0.018). No consistent trend was observed between the duration of LNG-IUD use and the prevalence of benign outcomes (Table 3).

To account for potential confounders, a logistic regression model was constructed, including LNG-IUD duration, age, BMI, and baseline hemoglobin. After adjustment, none of these variables were independently associated with benign breast disorders (Table 4).

Adjusted odds ratios with 95% confidence intervals from the multivariable logistic regression are illustrated in Supplementary Figure 2.

Discussion

This prospective cohort study provides important evidence regarding the prevalence and characteristics of benign breast abnormalities among LNG-IUD users. While most previous LNG-IUD safety studies have focused on malignancy, this study found that benign conditions-particularly simple cysts and fibrocystic changes-were frequently observed but were not associated with duration of device use. This distinction is clinically important because benign lesions, while not life-threatening, can affect women's perceptions of contraceptive safety and lead to discontinuation of, or hesitation to use, the device. This study documents the prevalence of non-proliferative benign lesions and reassures clinicians and patients that such findings are generally incidental rather than device-induced.

Table 1. Baseline characteristics of the study population

Characteristic	Total (n=80)	Benign breast disorder (n=57)	No benign disorder (n=23)	p-value
Age, years (mean ± SD)	47.2±4.4	47.5±4.2	46.5±4.8	0.42
BMI, kg/m² (mean ± SD)	28.1±3.9	28.3±4.1	27.7±3.6	0.61
Parity ≥2, n (%)	55 (68.7)	38 (66.7)	17 (73.9)	0.52
Baseline hemoglobin, g/dL	12.6±1.1	12.4±1.0	13.1±1.2	0.018*
Duration of LNG-IUD use, months	34.7±12.8	35.1±13.2	33.8±11.7	0.68

*: p<0.05, statistically significant, SD: Standard deviation, BMI: Body mass index, LNG-IUD: Levonorgestrel-releasing intrauterine device

Table 2. Distribution of benign breast disorders (n=57)

Lesion type	n (%)
Simple cysts	49 (61.3)
Fibrocystic changes	12 (15.0)
Fibroadenoma	1 (1.3)
Multiple lesions	22 (27.5)
Bilateral involvement	18 (22.5)

Table 3. Comparison of clinical variables between women with and without benign breast disorders

Variable	Benign disorder (n=57)	No disorder (n=23)	p-value
Age ≥45 years, n (%)	39 (68.4)	14 (60.9)	0.52
BMI ≥30 kg/m², n (%)	22 (38.6)	7 (30.4)	0.48
Hemoglobin <12 g/dL, n (%)	15 (26.3)	2 (8.7)	0.04*
LNG-IUD use ≥36 mo, n (%)	28 (49.1)	10 (43.5)	0.65

*: p<0.05, statistically significant, BMI: Body mass index, LNG-IUD: Levonorgestrel-releasing intrauterine device

Table 4. Multivariable logistic regression for predictors of benign breast disorders (n=18 complete cases)

Variable	Adjusted OR (95% CI)	p-value
LNG-IUD duration	0.44 (0.12-1.57)	0.21
Age (per year)	1.02 (0.87-1.18)	0.72
BMI (per kg/m²)	1.05 (0.90-1.23)	0.53
Hemoglobin (per g/dL)	0.81 (0.56-1.17)	0.26

OR: Odds ratio, CI: Confidence interval, LNG-IUD: Levonorgestrel-releasing intrauterine device, BMI: Body mass index

The current literature presents conflicting results regarding the association between LNG-IUD use and breast cancer. Dinger et al.[15] reported that they did not observe a significant increase in breast cancer risk in LNG-IUD users compared to copper IUD users in a large European cohort, supporting the safety of hormonal intrauterine systems. On the other hand, Goldštajn et al.[16] found a modest increase in breast cancer risk in those using combined hormonal therapy but acknowledged that the absolute risk remained low. These conflicting results reflect the ongoing debate regarding hormonal contraceptives and malignancy. The current findings contribute to this debate by focusing on benign pathologies that have been less systematically studied and by broadening the understanding of LNG-IUD safety.

The distribution of benign breast lesions detected in this cohort is consistent with prevalence patterns reported in general screening populations. El-Feky et al.[17] showed that cystic breast disease is among the most frequently reported incidental findings in ultrasonographic evaluations, particularly in women aged 40 and over. Similarly, Lohani et al.[18] reported no significant increase in long-term breast cancer risk in women with non-proliferative benign breast lesions such as simple cysts. The consistency between the findings of the present study and these reports suggests that benign breast findings detected in LNG-IUD users are more likely attributable to age and population-based background risk than to contraceptive exposure. This interpretation should be considered with particular caution due to the absence in the study of a control group that did not use LNG-IUDs; however, the observed prevalence rates, which overlap with age-matched reference cohorts, are reassuring in the context of an indirect comparison.

Possible biological mechanisms also support these observations. It has been previously reported that the effects of progestins on breast epithelium can vary depending on the hormonal context, receptor expression, and exposure level; they can exhibit proliferative effects in some conditions and inhibitory effects in others[19]. However, Zürcher et al.[20] showed that levonorgestrel released from intrauterine systems is associated with minimal systemic exposure compared to oral progestin formulations. This pharmacokinetic feature provides a biological explanation for the absence of either a dose-dependent or a duration-dependent relationship between LNG-IUD use and benign breast outcomes in the present study. Indeed, in additional analyses in which the duration of LNG-IUD use was divided into quartiles and a binary classification was performed using the median value, no trend was detected; these findings supported the main conclusion that the duration of device use did not affect benign breast outcomes.

From a patient counseling perspective, the reassurance provided by these findings offers a clinically significant contribution. Concerns about breast health are frequently raised during contraceptive counseling, particularly in women approaching perimenopause, when the possibility of breast pathology and the need for contraception arise simultaneously. Sanders et al.[21] demonstrated that anxiety about perceived breast health risks can influence women's contraceptive choices and lead to unnecessary abandonment of effective methods. In this context, the present study, which reveals that benign breast lesions are common but not associated with the duration of LNG-IUD use, facilitates the development of evidence-based counseling messages aimed at reducing unnecessary anxiety and supporting continuation of the method.

The present findings are also consistent with studies examining other hormonal contraceptive methods. Grandi et al.[22] evaluated the relationship between oral contraceptive use and fibrocystic breast disease and found no significant association. These results, considered together with the findings of the present study, point to a consistent pattern across hormonal contraceptive methods. Accordingly, it appears that neither systemically released nor locally released progestins significantly increase the frequency of benign breast pathologies. Obtaining similar results with different contraceptive methods reinforces the interpretation that detected benign breast lesions are largely age-related and incidental findings.

The psychological burden accompanying benign breast findings is another dimension that should not be overlooked in clinical practice. Gram et al.[23] reported that a significant proportion of women with benign breast findings during screening programs develop persistent anxiety, which often leads to unnecessary additional investigations. The current study emphasizes the importance of addressing such findings in an appropriate clinical context during contraceptive counseling. Clearly stating that most benign breast lesions are not related to LNG-IUD use can contribute to reducing patient anxiety and preventing subsequent unnecessary investigations, thus improving the quality of care while reducing the burden on healthcare services.

This study has several methodological strengths. The adoption of a prospective design, the systematic application

of standardized breast imaging according to the BI-RADS classification, and the blinded radiological evaluation enhance the internal validity of the findings. The consensus review of imaging results by two senior radiologists further reduced inter-observer variability. The participant inclusion and exclusion process is detailed in Supplementary Figure 1, and adjusted results from multivariate regression analyses are shown in Supplementary Figure 2 to ensure transparency in reporting. These methodological features increase the reliability of the results and strengthen the comparability of the findings with the international literature.

Study Limitations

However, some limitations must be considered. The lack of systematic breast imaging prior to LNG-IUD placement restricts definitive differentiation of newly developed from pre-existing lesions. Furthermore, the exclusion of a control group of individuals not using LNG-IUDs prevents direct comparison between users and non-users. Although stratified analyses were performed based on the duration of LNG-IUD use, the limited number of complete cases, particularly in multivariate models, may have reduced the power to detect weaker associations. Although image-based classification was rigorously applied, histopathological confirmation could not be obtained for all lesions.

This prospective cohort study reveals that benign breast disease is common among LNG-IUD users, but these findings are not associated with the duration of device use. Despite the current methodological limitations, the consistency of the results with age-matched, population-based prevalence data, together with additional analyses, increases confidence in the findings. To confirm these preliminary findings and to clarify the risk of rare but clinically significant malignancies, larger-scale, multicenter studies including pre-treatment breast evaluations, appropriate control groups, and long-term follow-up are needed.

Conclusion

This prospective cohort study shows that benign breast abnormalities-particularly simple cysts and fibrocystic changes-are common among LNG-IUD users, but these findings are not related to the duration of device use. The observed prevalence rates are consistent with the background risk associated with age, suggesting that these lesions may be incidental findings rather than related to LNG-IUD exposure. Although the lack of pre-treatment breast imaging, the absence of a non-user control group, and the relatively limited sample size limit the strength of the evidence, the current findings provide a reassuring framework for contraceptive counseling by demonstrating that benign breast outcomes are common but are not linked to LNG-IUD use. To confirm these results and more clearly address the question of the risk of rare but clinically significant malignancies, multicenter studies encompassing larger populations and including pre-treatment assessments and long-term follow-up are needed.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee (approval no: 492, date: 08.07.2025).

Informed Consent: Prior to involvement in the study, written informed consent was obtained from all participants. All participants provided written consent for the use of anonymized data in scientific publications.

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Footnotes

Authorship Contributions

Surgical and Medical Practises: M.Ç., T.Y.U., Concept: M.Ç., M.B.D., Design: M.Ç., T.Y.U., Data Collection or Processing: T.Y.U., M.B.D., K.K., Analysis or Interpretation: İ.U., Ö.B.Ç., Literature Search: Ö.B.Ç., Writing: M.Ç., M.B.D., Ö.B.Ç.

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Supplementary Figure 1 and 2: https://d2v96fxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/content-images/267e04d9-325a-4b72-a125-3331b6702f16.pdf

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