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TABLE OF CONTENTS

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HbA1c=glycated hemoglobin; T2D=type 2 diabetes.
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‡ The landing page of mounjaro.ca is open to the general public. To access healthcare provider-directed information, you will need to log in. Patients will require a DIN to access patient-directed information.

Reference: Current Mounjaro Product Monograph. Eli Lilly Canada Inc.

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Dr. Anil Gupta, a graduate of the University of Toronto's Faculty of Medicine, is a primary care physician, researcher, and author with over 19 years of experience as a principal investigator in more than 150 clinical trials. His passion for clinical research led him to play a key role in groundbreaking studies on COVID-19 treatments during the pandemic. Dr. Gupta was the lead author of two major publications in the *New England Journal of Medicine (NEJM) and Journal of the American Medical Association (JAMA)*, focusing on the efficacy and safety of the SARS-CoV-2 neutralizing antibody, sotrovimab. Additionally, he contributed as a lead collaborator to the KidCOVE study evaluating the mRNA-1273 vaccine for children aged 6–11. His extensive research background includes a trial on Vitamin B-12 deficiency in South Asians published in CFPC May,2004. Reflecting on his work, Dr. Gupta takes pride in demonstrating that family doctors can make significant contributions to clinical research, proving that groundbreaking studies are not limited to specialists.

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Comparative Study of Ferrous Fumarate, Ferrous Ascorbate, and Polysaccharide Iron for Treating Iron Deficiency Anemia in Adults

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Iron deficiency anemia (IDA) is a highly prevalent condition encountered in clinical practice and represents a major global health concern, affecting an estimated 1.92 billion individuals worldwide. Despite its prevalence and the availability of various oral iron formulations with wide cost variations, comparative data on their efficacy and tolerability remain limited.

This randomized, open-label trial conducted across two centres evaluated the efficacy, tolerability, and adherence of three oral iron supplements in improving hemoglobin and ferritin levels in adults with IDA. The study compared ferrous fumarate (Eurofer, 100 mg elemental iron, $15.87 for 90 tablets), ferrous ascorbate (EBMfer, 100 mg elemental iron, $68.97 for 90 tablets), and polysaccharide iron (FeraMAX, 150 mg elemental iron, $77.97 for 90 tablets). A total of 111 participants aged ≥18 years were randomly assigned into one of three treatment groups and monitored over a 12-week period.

Both ferrous fumarate (p=0.001) and ferrous ascorbate (p<0.001) demonstrated significantly greater hemoglobin and ferritin levels compared to polysaccharide iron. Specifically, ferrous fumarate led to mean increases in hemoglobin and ferritin of 11.59 g/L (95% confidence interval [CI]: 7.87–15.3, standard deviation [SD]: 10.7) and 19.21 µg/L (95% CI: 7.82–28.6, SD: 29.8), respectively. Ferrous ascorbate showed mean increases in hemoglobin and ferritin levels of 17.14 g/L (95% CI: 13.5–20.8, SD: 10.7) and 23.51 µg/L (95% CI: 16.5–30.5, SD: 20.3), respectively. Polysaccharide iron showed mean increases in hemoglobin and ferritin of 3.56 g/L (95% CI: -0.06–7.18, SD: 10.4) and 3.21 µg/L (95% CI: -0.07–6.48, SD: 9.39), respectively.

Adverse events occurred more frequently with ferrous fumarate (13 events) compared with ferrous ascorbate (8 events) and polysaccharide iron (6 events). The most commonly reported side effects across all groups were constipation and bloating, well-documented side effects of iron supplements.

These findings demonstrate that ferrous fumarate and ferrous ascorbate significantly outperformed polysaccharide iron in improving hemoglobin and ferritin levels. Given its lower cost and comparable efficacy, ferrous fumarate may be the most cost-effective option and warrants consideration in updates to Canadian treatment guidelines.

Introduction

Iron deficiency anemia (IDA) remains a major global health concern, affecting over 1.92 billion individuals and contributing significantly to morbidity and diminished quality of life.[1] This condition disproportionately impacts vulnerable populations, including females of reproductive age, children, and older adults, leading to impaired cognitive and physical performance.[2] IDA can arise from various causes, including blood loss and dietary factors.[2]

In our clinical experience, IDA is a frequently encountered condition. We have observed significant variability in how patients with IDA respond to different iron supplements, which prompted us to closely examine the existing literature.

Despite the high prevalence of IDA and the availability of multiple oral iron formulations, comparative data on their efficacy remains limited. Among the studies that do exist, several have reported notable differences in outcomes. However, many of these studies were published in lesser-known medical journals, often years ago, and may not be widely recognized or referenced.

A 2004 trial revealed that ferrous fumarate significantly improved hemoglobin levels (28.4 g/L) compared to (6 g/L) with polysaccharide iron, though it was associated with a higher incidence of gastrointestinal side effects.[3] Similarly, a 2017 study in pediatric patients reported anemia resolution in 29% of children treated with ferrous sulfate, whereas only 6% of those receiving polysaccharide iron achieved resolution.[4]

In Canada, clinical guidelines for IDA management recommend selecting a supplement based on cost and tolerability rather than efficacy, despite evidence suggesting otherwise.[5-8] Commonly reported side effects of oral iron supplements include constipation, nausea, vomiting, abdominal discomfort, and dark or black stools.[5,7]

This study aimed to address knowledge gaps by comparing the effectiveness of three ferrous salts—ferrous fumarate (EuroFer), ferrous ascorbate (EBMFer), and polysaccharide iron (FeraMax)— in improving hemoglobin and ferritin levels in adults with IDA over a 12-week period. These formulations were selected because ferrous fumarate and polysaccharide iron are commonly recommended options in Canadian practice, while ferrous ascorbate, a formulation commonly used in other regions, has shown promising results and is also available in Canada.

Materials and Methods

Study Design

A randomized, open-label, parallel-group trial was conducted between February and December 2024 in a clinical practice setting at two family practices located in northwest Toronto and the Peel region—areas known for their highly diverse populations. Participants were recruited through referrals from local physicians and community advertisements.

The study received approval from the Advarra Central Institutional Review Board (CIRBI). Written informed consent was obtained from all participants before enrolment. The study was conducted and analyzed in accordance with the Consolidated Standards of Reporting Trials (CONSORT).

Following a one-week screening period, eligible participants were randomly assigned in a 1:1:1 ratio to receive one of the three iron supplements once daily for 12 weeks: ferrous fumarate (100 mg elemental iron, $15.87 for 90 tablets), ferrous ascorbate (100 mg elemental iron, $68.97 for 90 tablets), or polysaccharide iron complex (150 mg elemental iron, $77.97 for 90 tablets). Randomization was stratified by treatment arm using block randomization to ensure balanced group allocation. Treatment assignments were generated using a predefined, computer-generated randomization sequence. Study medications were obtained from a local pharmacy and provided to participants at no cost.

At the baseline visit, participants received standardized instructions on how to take their assigned iron supplements. All participants were advised to take one tablet daily. Those in the ferrous fumarate and polysaccharide iron groups were instructed to take their supplement on an empty stomach along with a source of vitamin C—such as orange juice, lemon water, or an over-the-counter vitamin C supplement—to enhance absorption. Participants in the ferrous ascorbate group were informed that additional vitamin C was not necessary because it is already included in the formulation.

Hemoglobin and ferritin levels were measured at baseline and at week 12, marking the end of the study. One week after the baseline visit, participants received a follow-up phone call to monitor for adverse effects and reinforce adherence. Participants who experienced side effects were offered the option of switching to alternate-day dosing. Throughout the study, participants were encouraged to contact the research staff if they experienced any adverse effects. At the final visit (week 12), participants were instructed to return any unused medication for pill counting to assess adherence. All reported adverse events were documented.

Inclusion and Exclusion Criteria

Inclusion Criteria:

Adults aged ≥18 years with confirmed IDA, defined as hemoglobin levels of ≤135 g/L for males and ≤120 g/L for females, and serum ferritin levels of <30 µg/L) were eligible for inclusion. The initial ferritin cutoff of <15 µg/L was updated to <30 µg/L based on a Canadian consensus statement.

Exclusion Criteria
1. Medical Conditions:
• Hemoglobin level of ≤80 g/L
• History of hematological disorders (e.g., aplastic anemia or megaloblastic anemia)
• Chronic renal disease, inflammatory disorders, or severe chronic conditions affecting safety
• History of intestinal malabsorption, hemochromatosis, or gastrointestinal surgery
• Significant bleeding or history of occult blood in stool
• Severe psychological disorders that may interfere with study participation
2. Iron Supplementation:
• Use of any other oral or intravenous iron supplements during the study
3. Prohibited Medications:
• Use of proton pump inhibitors, cholestyramine, colestipol, or initiation of anticoagulants within the past 6 months
4. Blood Transfusion/Donation/Intravenous Iron Therapy:
• History of blood transfusion, blood donation, or intravenous iron therapy within the past 4 months
5. Pregnancy and Conception:
• Pregnant individuals, those actively trying to conceive, or those undergoing fertility treatment
6. Hypersensitivity:
• Known or suspected hypersensitivity to iron or any formulation components
7. Surgical and Blood Sampling Considerations:
• Recent or planned surgery or difficulties with blood sampling
8. Alcohol/Drug Abuse:
• Evidence of alcohol or drug abuse likely to interfere with study adherence

Table 1. Summary of Exclusion Criteria for the Iron Supplementation Clinical Trial; *courtesy of Anil Gupta, MD, CCFP, FCFP, Amisha Gandhi, Ind. Elec. Eng., Vishwas Kini, MD, CCFP, Kira Gupta-Baltazar, BSc (Hons) and Karen Tu, MD, CCFP, FCFP.*

Exclusion Criteria:

Outlined in **Table 1**, exclusion criteria included severe anemia (hemoglobin ≤80 g/L), hematological disorders, chronic illnesses, pregnancy, and known hypersensitivity to iron. The study protocol is provided in Supplement 1.

Outcome Measures

The primary outcome was the change in hemoglobin levels from baseline to 12 weeks between participants receiving ferrous fumarate and those receiving polysaccharide iron.

Secondary outcomes included comparisons of changes in hemoglobin levels from baseline to 12 weeks between the ferrous ascorbate and polysaccharide iron groups, changes in ferritin levels across all three groups, and evaluations of tolerability and discontinuation rates among the three oral formulations.

Sample Size

The study was designed with a power of 80% and a significance level of $\alpha=0.05$ to detect a large effect size (0.7). To account for potential dropouts and missing data, the sample size was increased from 99 to 111 participants to ensure robust analysis.

Parameters	Ferrous Fumarate (*Eurofer*)	Ferrous Ascorbate (*EBMfer*)	Polysaccharide Iron (*FeraMAX*)
Age range (years)	18–75	20–83	22–82
Mean age (years)	47	42	47
Age distribution (years)			
(18–30)	4	5	4
(31–50)	19	24	18
(51–70)	5	5	8
(≥71)	4	1	4
Male participants	7 (20.6%)	3 (8.6%)	5 (14.7%)
Female participants	27 (79.4%)	32 (91.4%)	29 (85.3%)
Baseline mean hemoglobin (g/L)	112.06	107.4	111.56
Baseline mean ferritin (ug/L)	15.21	11.77	13.44

Table 2. Demographic and Baseline Hemoglobin and Ferritin Parameters by Iron Supplementation Group; *courtesy of Anil Gupta, MD, CCFP, FCFP, Amisha Gandhi, Ind. Elec. Eng., Vishwas Kini, MD, CCFP, Kira Gupta-Baltazar, BSc (Hons) and Karen Tu, MD, CCFP, FCFP.*

Randomization and Allocation of Intervention Products

Statistical Methods

Statistical analyses were performed using jamovi 2.3.28, alongside R (version 4.1) and its associated statistical packages. Due to violations of normality confirmed by the Shapiro-Wilk test, non-parametric methods were applied. Specifically, the Kruskal-Wallis test and Mann-Whitney U test were employed for between-group comparisons.[9-11]

Results

Participant Flow

Of the 196 individuals screened, 111 were randomized into the study. A total of 103 participants (88 females and 15 males) completed all study procedures. **Figure 1** presents the CONSORT diagram, outlining participant flow through the stages of enrolment, allocation, follow-up, and analysis. **Table 2** includes the demographic data and baseline hemoglobin and ferritin levels for each iron supplementation group.

Primary Outcome

Participants receiving ferrous fumarate experienced a mean hemoglobin increase of 11.59 g/L (95% confidence interval [CI]: 7.87–15.3, standard deviation [SD]: 10.7), compared to 3.56 g/L (95% CI: -0.06–7.18, SD: 10.4) in the polysaccharide iron group. The mean difference of 8.03 g/L significantly favoured ferrous fumarate (p=0.001) (**Table 3**).

Secondary Outcomes

Secondary outcomes are presented in **Table 3**. Participants receiving ferrous ascorbate experienced a mean hemoglobin increase of 17.14 g/L (95% CI: 13.5–20.8, SD: 10.7), compared to 3.56 g/L (95% CI: -0.06–7.18, SD: 10.4) in the polysaccharide iron group. The mean difference of 13.58 g/L favoured ferrous ascorbate (p<0.001).

Ferritin levels increased by 19.21 µg/L (95% CI: 7.82–28.6, SD: 29.8) with ferrous fumarate, 23.51 µg/L (95% CI: 16.5–30.5, SD: 20.3) with ferrous ascorbate, and 3.21 µg/L (95% CI: -0.07–6.48, SD: 9.39) with polysaccharide iron. The mean increase in ferritin was significantly greater for ferrous fumarate compared to polysaccharide iron, with a difference of 16.00 µg/L (p<0.001), and for ferrous ascorbate compared to polysaccharide iron, with a

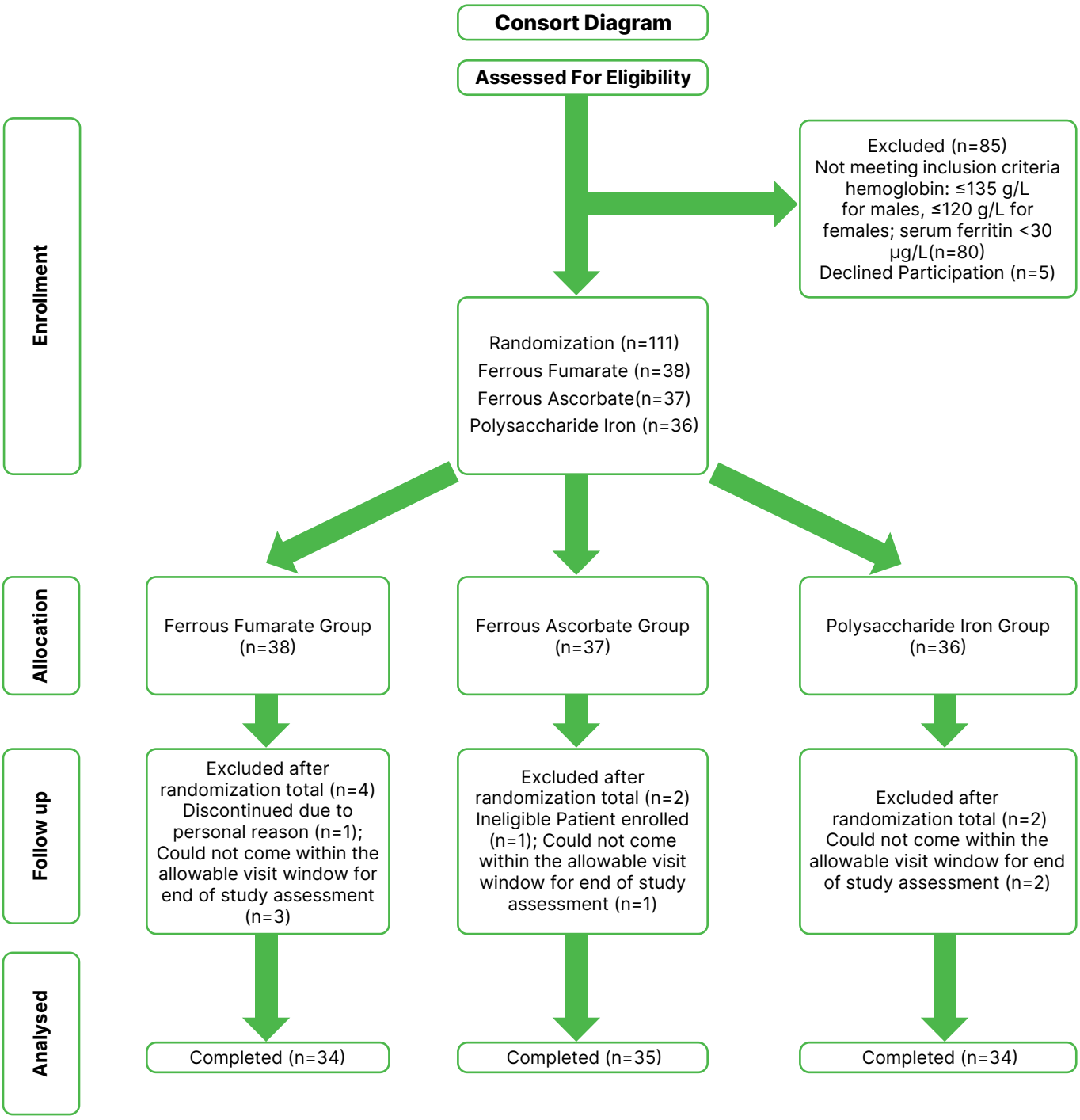

Figure 1. CONSORT Diagram; *courtesy of Anil Gupta, MD, CCFP, FCFP, Amisha Gandhi, Ind. Elec. Eng., Vishwas Kini, MD, CCFP, Kira Gupta-Baltazar, BSc (Hons) and Karen Tu, MD, CCFP, FCFP.*

	Mean Hemoglobin Level (*g/L*) at Baseline Visit	Mean Hemoglobin Level (*g/L*) at End of Study Visit	Mean Change in Hemoglobin Level (*g/L*) from Baseline to End of Treatment	Mean Ferritin Level (*µg/L*) at Baseline Visit	Mean Ferritin Level (*µg/L*) at End of Study Visit	Mean Change in Ferritin Level (*µg/L*) from Baseline to End of Treatment	Mean Compliance (*%*)	Reported Adverse Events
Ferrous Fumarate (Eurofer) (n=34)	112.06	123.65	11.59	15.21	34.42*	19.21*	79	13
Ferrous Ascorbate (EBMfer) (n=35)	107.4	124.54	17.14	11.77	35.29	23.51	79	8
Polysaccharide Iron (FeraMAX) (n=34)	111.56	115.12	3.56	13.44	16.64	3.21	89	6

Table 3. Comparison of Hemoglobin, Ferritin, Compliance and Adverse Events Across Iron Supplement Groups from Randomization to End of Study; *courtesy of Anil Gupta, MD, CCFP, FCFP, Amisha Gandhi, Ind. Elec. Eng., Vishwas Kini, MD, CCFP, Kira Gupta-Baltazar, BSc (Hons) and Karen Tu, MD, CCFP, FCFP.*

*****One participant had a post-treatment ferritin level of 197 µg/L, which could be attributed to an acute-phase reaction and may have potentially skewed the average change in ferritin levels. If this outlier is excluded, the average ferritin level (µg/L) at the end of the study would be 29.49, and the average change in ferritin (µg/L) from baseline to the end of treatment would be 13.93.

difference of 20.30 µg/L ($p<0.001$). The difference between ferrous ascorbate and ferrous fumarate was 4.30 µg/L ($p>0.05$), indicating no statistically significant difference.

Compliance Rates

The highest compliance was observed in the polysaccharide iron group (89%), followed by both the ferrous ascorbate and ferrous fumarate groups, each at 79%.

Adverse Events

Adverse events were most frequently observed from the ferrous fumarate group (n=13), followed by ferrous ascorbate(n=8), and polysaccharide iron (n=6). Constipation and bloating were reported across all groups, with abdominal pain and dark stool reported specifically with the ferrous salt formulations.

Discontinuations

Study discontinuations included four participants from the ferrous fumarate group, one from the ferrous ascorbate group, and two from the polysaccharide group. No discontinuations were attributed to adverse events, and no participants were lost to follow-up.

Discussion

This study demonstrates that ferrous salts—specifically ferrous ascorbate (EBMfer) and ferrous fumarate (EuroFer)—were more effective than polysaccharide iron (FeraMax) in improving hemoglobin and ferritin levels in adults with IDA. Notably, ferrous ascorbate was superior to ferrous fumarate in increasing hemoglobin levels.

Tolerability and compliance were highest in the polysaccharide iron group. However, with compliance rates of 79% and 89% for the ferrous salts and polysaccharide iron, respectively, all three formulations were generally well tolerated. Despite lower compliance and more frequent adverse events with the ferrous salts, they still outperformed the polysaccharide iron in improving hematologic parameters.

Although few clinical trials have directly compared the efficacy of different oral iron supplements, our findings align with the limited available evidence suggesting that ferrous salts are more effective than polysaccharide iron formulations in raising hemoglobin and ferritin levels.

We selected three oral iron supplements available in Canada, based on their domestic recommendations and international usage. Current Canadian guidelines advise choosing supplements based on cost and tolerability rather than efficacy. In our study, ferrous ascorbate and polysaccharide iron were similarly priced, whereas ferrous fumarate was approximately one-quarter the cost of either.

To our knowledge, this is the largest randomized interventional study comparing different classes of oral iron formulations. However, not all formulations were included. Additional research is needed to evaluate other commonly used preparations. Moreover, as ferritin was the sole iron marker assessed, it may not provide a comprehensive assessment of iron status.

The study population was drawn exclusively from northwest Toronto and the Peel region, which may limit the generalizability of the findings to the broader Canadian population.

Additionally, participants in the ferrous ascorbate group had lower baseline hemoglobin levels compared to the other two groups, which may have contributed to the greater increase observed in this group.

Conclusion

Ferrous salts—specifically ferrous ascorbate (EBMfer) and ferrous fumarate (EuroFer) —were significantly more effective than polysaccharide iron (FeraMax) in increasing both hemoglobin and ferritin levels. Ferrous ascorbate also demonstrated superior efficacy over ferrous fumarate in improving hemoglobin levels. These findings may inform treatment selection for IDA by integrating considerations of efficacy, cost, and tolerability.

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The study is registered on **ClinicalTrials.gov** (ID: NCT06303531) and approved by the Advarra Institutional Review Board, ensuring compliance with ethical and regulatory guidelines.

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Awiqli® (insulin icodec injection) is indicated for the once-weekly treatment of adults with diabetes mellitus to **improve glycemic control**.[6]

Please see the respective Product Monographs for complete dosing and administration information.[2,4-6]

Consult the Product Monographs at **WegovyPM-E.ca**, **OzempicPM-E.ca**, **RybelsusPM-E.ca**, and **AwiqliPM-E.ca** for more information relating to contraindications, warnings and precautions, conditions of clinical use, adverse reactions, drug interactions, and dosing information, which have not been discussed in this piece.

Product Monographs are also available by calling us at 1-800-465-4334.

* Comparative clinical significance is unknown.
† This landing page is open to the general public.
‡ Comparative clinical significance not established.
BMI, body mass index; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

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Acne Therapies for the Primary Care Physician: What's New and What's Practical

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Acne vulgaris is the most common dermatologic condition worldwide, affecting people across a broad range of ages and skin phototypes. There are a variety of pathophysiological processes involved in the formation of acne lesions, with available anti-acne therapies targeting such pathways. Herein, we provide a review of important acne treatment classes and present novel topical, oral and energy-based interventions.

Introduction

Acne vulgaris (AV) is a chronic inflammatory dermatosis involving the pilosebaceous unit, whereby increased sebum production, follicular hyperkeratinization, *Cutibacterium acnes* (previously *Propionibacterium acnes*) proliferation, and localized, heightened immune responses result in the development of acne lesions.[1,2] AV is thought to affect more than 80% of adolescents and young adults, forming a substantial proportion of both the dermatologist's and general practitioner's caseload, and is frequently treated in primary care settings by non-dermatologists.[3,4] Thus, it is of utmost importance that primary care providers stay up to date with acne management strategies and expanding therapeutic options.

Several options are available to treat AV, ranging from conservative measures such as cleansers, moisturizers, and skin care products, to topical mono- and combination therapies including benzoyl peroxide, antibiotics and/or retinoids. Additional treatments include oral therapies, such as antibiotics, hormonal agents and isotretinoin, as well as energy-based devices.[5] Given the plethora of available and evolving modalities, and the essential role of the primary care provider in the management of patients with acne, a robust therapeutics framework as outlined below offers real-world practical value.

Conservative Measures and Lifestyle Modifications

Given increasing interest in targeted skin care regimens, and growing recognition of the role of a healthy epidermal barrier in the management of various dermatological disorders, the medicalization of skin care is crucial in the overall management of AV.[6] Recent studies have demonstrated the efficacy of over-the-counter (OTC) acne skin care products, many of which contain Food and Drug Association (FDA)-monographed ingredients. Although these ingredients can be non-prescription, they have been shown to alter both the structure and function of acne-prone skin.[7] Combining a proper skincare regimen with AV treatments may decrease irritation and support a healthy skin barrier, improving treatment adherence and outcomes.[8] Moreover, allowing patients to select their own skincare products can provide them with a sense of control in managing their disease, which may reduce the psychological sequelae of acne.[7]

Dermocosmetics are non-medicinal products with both cosmetic and active ingredients that improve cutaneous disorders, and more specifically acneceuticals, which play an important potential role in acne therapy specifically, have been embraced in Europe for decades. However, their use remains limited in North America, despite their ability to target three of the four central pathophysiological processes implicated in acne pathophysiology (keratolytic, antibacterial, and anti-inflammatory) (**Table 1**). Notably, recent data supports the

use of conservative measures including the use of pH-adjusted, gentle cleansers, which act to promote a healthy skin barrier and contribute to the healing or attenuation of inflammatory skin conditions.[9-12] Importantly, lipid-free cleansers have been found to be most appropriate for use in acne-prone skin as they are less irritating and have a pH similar to that of the stratum corneum.[11] The latest guidelines conditionally recommend the use of topical salicylic and azelaic acids in the management of AV, given their ability to target three of the four central pathophysiological processes implicated in acne pathophysiology (keratolysis, antibacterial, and anti-inflammatory).[13] Other common agents, namely oral or topical niacinamide, topical tea tree oil, topical green tea, topical witch hazel, oral pantothenic acid, oral or topical zinc, topical glycolic acid, sulphur, sodium sulfacetamide, and resorcinol, have insufficient clinical evidence to formulate recommendations at this time.[13]

Multiple studies have explored the relationship between diet and acne, with the notion that acne as an inflammatory pathology is at the centre of it.[14] However, the link between nutrition and acne continues to be extensively debated and remains controversial.[15] Research has found that plant-based foods may improve inflammatory skin diseases by supporting the gut microbiome, exerting anti-inflammatory effects, providing barrier support, and improving glycemic control. Key nutrients contributing to these effects include riboflavin, vitamin B12, vitamin A, omega-3 fatty acids, protein, fibre, antioxidants, and phytonutrients.[16,17] Studies investigating omega-3 fatty acid levels in acne patients found that many patients had insufficient omega-3 levels, and that normalization of these levels was associated with a significant improvement in acne severity.[18] Additionally, omega-3 indices were increased by means of consuming a Mediterranean diet or through oral supplementation with omega-3 fatty acids.[18] Moreover, daily consumption of omega-3 has been shown to decrease the mucocutaneous side effects of isotretinoin (cheilitis, xerosis, nose dryness), thereby increasing tolerability, compliance, and overall outcomes.[19,20] Furthermore, use of oral or topical probiotics, symbiotics, or postbiotics has also been shown to restore skin homeostasis, improving acne and other inflammatory skin conditions.[17] However, chocolate consumption was associated with a statistically significant

Mechanism of Action	Active Ingredients
Keratolytic	• Azelaic acid • Alpha and beta hydroxyacids • Retinol derivates • Bakuchiol • Silymarin • Sulfur
Antibacterial	• Azelaic acid • Niacinamide • Zinc • Green tea • Resveratrol • Silymarin • Bakuchiol • Soy • Probiotics • Retinaldehyde • Sodium hypochlorite • Tea tree oil
Anti-inflammatory	• Niacinamide • Salicylic acid • Azelaic acid • Bakuchiol • Linoleic acid • Lactobacillus • Aloe vera • Green tea • Cannabidiol • Zinc • Resveratrol • Silymarin • Sodium hypochlorite • Tea tree oil
Sebum reduction	• Niacinamide • Zinc • Green tea • Silymarin • Bakuchiol • Linoleic acid • Clay • Soy • Resveratrol
Barrier repair	• Niacinamide • Hyaluronic acid • Alpha and beta hydroxy acids • Glycerin • Colloidal oatmeal • Panthenol • Ceramides • Shea butter

Table 1. Acneceuticals; *adapted from Baldwin et al.*[7]

Agent	Mechanism	Administration
Topical Therapies		
Winlevi® Clascoterone 1% cream, available in 30 and 60 g tubes	Topical anti-androgen receptor inhibitor	AM + PM
Cabtreo® Benzoyl peroxide 3.1% + clindamycin phosphate 1.2% + adapalene 0.15% gel, available as a 50 g pump	Topical antibiotic and third-generation retinoid	PM
Arazlo® Tazarotene 0.045% lotion, available in 45 g tubes	Topical third-generation retinoid	PM
Aklief® Trifarotene 0.005% cream, available in 75 g pumps	Topical fourth-generation retinoid	PM
Oral Therapies		
Epuris® Isotretinoin-lidose capsules, available in 10, 20, 30, and 40 mg capsules	Oral systemic retinoid with lipid encapsulation	AM or PM, with food (no need for high-fat content)
Absorica® Isotretinoin-lidose capsules, available in 8, 16, 24, and 32 mg capsules	Oral systemic retinoid with lipid encapsulation in a micronized formulation	AM or PM, food not required

Table 2. Novel Topical and Oral Acne Therapies; *courtesy of Santina Conte, MD and Monica K. Li, MD, FRCPC, FAAD.*

intensification of acne lesions even in the presence of an anti-inflammatory diet.[21] Despite this, the current clinical evidence in dietary influences on acne remains insufficient to draw firm conclusions regarding the consumption of a low dairy diet, low whey diet, omega-3 fatty acids, and chocolate. Finally, acne is significantly influenced by glycemic load, with an established association between high glycemic load foods and severe acne secondary to insulin and insulin-like growth factor 1 levels, which stimulate sebum production and androgen hormone release.[22-25] Common high glycemic index foods include bread (white, whole wheat), naan (white, whole wheat), white, sticky, or jasmine rice, potatoes, and bananas, amongst others. Importantly, dietary counselling along with the consumption of low glycemic level foods has been shown to improve acne severity and lesions,[22] although conflicting evidence continues to exist in the current literature.

Topical Therapies

According to the most recent *Journal of the American Academy of Dermatology (JAAD)* acne guidelines (January 2024), topical benzoyl peroxide (BP) is strongly recommended for the management of AV.[13] BP is generally regarded as an effective first-line therapy for AV whether used as monotherapy or in combination with a topical antibiotic and/or topical retinoid.[26] Available both OTC or by prescription, BP targets three of the four major acne pathophysiological pathways: it exhibits bactericidal activity against *C. acnes*, as well as possessing mild sebostatic and keratolytic properties, which are potentiated when used in combination with other topical therapies.[27] There is no current literature to suggest the development of drug resistance with BP use.[28]

Several innovative novel therapies for AV have come to market in recent years (**Table 2**). Clascoterone 1% cream (Winlevi®) is a first-in-class topical androgen receptor inhibitor approved for the treatment of

acne in patients 12 years and older.[29] It has demonstrated efficacy and is well-tolerated regardless of acne severity, age, gender, and ethnicity.[29-31] Expert panels emphasized that clascoterone should be used in conjunction with other acne treatments—such as in conjunction with topical retinoids or systemic therapies such as isotretinoin or spironolactone—to achieve optimal results, as acne is best targeted by multiple mechanisms.[29] Reinforcing the importance of multimodal therapy in the management of AV, Cabtreo® is a novel triple combination gel containing 1.2% clindamycin phosphate, 0.15% adapalene and 3.1% BP.[32] Studies have demonstrated that this agent offers superior efficacy compared to vehicle or unimodal therapy with BP, adapalene, or clindamycin topicals, with good overall treatment tolerance.[32,33] Finally, there are two relatively recent topical retinoid additions to the acne armamentarium: tazarotene lotion (Arazlo®) and trifarotene cream (Aklief®). Arazlo® is a third-generation retinoid with polymeric emulsion technology and a honeycomb hydrating base designed to reduce irritation.[34] It has demonstrated efficacy and safety in treating of both acne and acne-induced post-inflammatory hyperpigmentation.[35-38] Aklief®, the sole fourth-generation topical retinoid-based formulation, selectively targets the most common retinoid acid receptor isotype (RAR-γ) in the epidermis. It has also demonstrated notable success in treating mild-to-moderate acne.[39-42] Most importantly, it has demonstrated clinical efficacy in reducing atrophic acne scars and acne-induced post-inflammatory hyperpigmentation, thus treating acute acne lesions and their sequelae, with potent anti-inflammatory effects.[41,43] Moreover, while both Arazlo® and Aklief® are effective for treating truncal acne, Aklief® holds a specific an on-label indication for this use.[40,44] A systematic review of randomized controlled trials comparing clascoterone, trifarotene, or tazarotene with vehicle concluded that no significant differences in efficacy were observed between the three molecules after 12 weeks of treatment in patients with moderate-to-severe acne, suggesting similar overall efficacy.[45] Thus, differences in dosing schedule, mechanism of action, accessibility/cost, and tolerability profiles become key factors determining prescription selection.

Oral Therapies

Multiple oral therapies are available for managing AV, such as antibiotics, retinoids, oral contraceptive pills, and aldosterone antagonists. Current guidelines recommend the use of isotretinoin for patients with severe acne, those unresponsive to standard treatment with oral or topical therapies, or those experiencing psychosocial burdens or scarring. Since its initial availability on the market, newer formulations of isotretinoin, namely Epuris® and Absorica® have become available. Historically, Accutane® required administration alongside a high-fat meal to ensure proper absorption, potentially leading to issues with patient adherence.[46] Epuris®, a lidose-coated form of isotretinoin, uses lipid encapsulation technology to enhance drug absorption, though it still recommends consumption with food, albeit not necessarily of high-fat content.[46] However, Absorica® and AbsoricaLD®, the latest form of lidose-isotretinoin in a micronized formulation, enhances drug absorption and maintains consistent serum isotretinoin levels regardless of gastrointestinal contents, making it the only on-label form of isotretinoin that can be taken on an empty stomach.[47] Before initiating isotretinoin therapy, baseline assessments should include liver enzyme tests, lipid panels, and pregnancy status in applicable individuals. Monthly pregnancy tests should be performed throughout treatment for individuals with childbearing potential. If baseline alanine aminotransferase (ALT) and triglyceride levels are normal, tests should only be repeated after the peak dose is reached, with tests typically obtained one month after starting the peak dose, or typically after completion of a total of two months of isotretinoin therapy.[48] If results remain normal upon reaching the peak dose, further monitoring is not required. However, if abnormalities are detected, or if the patient is known to have dyslipidemia, periodic monitoring should continue. Most importantly, for patients with childbearing potential, pregnancy prevention is mandatory given isotretinoin's teratogenic capacity.

Laser and Light Therapies

Lasers and energy-based technologies are other treatment modalities used for acne given their precise and non-invasive nature.[49] More recently, the efficacy of light- and laser-based devices have demonstrated efficacy in managing AV via reducing inflammatory lesions by

targeting *C. acnes*, suppressing sebaceous gland activity, and modulating inflammation.[50] Notably, the novel 1726 nm laser, marketed under the name AviClear™, is the first and only FDA-approved laser treatment for mild to severe acne. This laser targets acne by inducing necrosis and thereby suppressing sebaceous gland activity. Clinical use has shown considerable lesion reduction with good tolerability and minimal side effects.[51,52] However, this treatment has limitations. Patients typically require a series of three treatments, with the total cost averaging CAD $3000–$5000. Access to such therapy may vary geographically, given that it is largely offered by dermatologists or aesthetic medicine providers. Of note, some patients have reported the procedure to be painful, with prolonged post-procedure edema and erythema, which may negatively impact the patient experience. Despite these limitations, the AviClear™ laser may be an effective alternative for patients who would prefer to avoid, have not responded to, or cannot tolerate topical or systemic acne therapies.[53]

Special Clinical Considerations – Adult Female Acne

While acne is typically regarded as a disease of adolescence, it remains prevalent throughout adulthood, especially among women.[54] Coined "adult female acne" (AFA), it can also result in scarring and dyspigmentation, impacting psychosocial health. AFA is frequently driven by an excess in androgens, which stimulate sebum production and the production of inflammatory cytokines.[55] Importantly, standard acne treatments typically do not treat AFA, as they do not address the patient's hormonal profile. In contrast, AFA typically responds very well to systemic anti-androgen therapies. Currently, four major anti-androgen treatments are available to treat AFA. Hormonal contraceptives, most notably the oral contraceptive pill (OCP), provide an anti-androgenic effect through an estrogen-mediated decrease in circulating free testosterone.[56,57] Progestins exhibit variable androgenic and anti-androgenic effects, potentially resulting in acne exacerbation. Notably, progestin-only pills should be avoided in acne-prone patients given their inherent risk of worsening the patient's skin. Otherwise, fourth-generation OCPs, namely Diane®-35 (cyproterone acetate), Yasmin®, and Yaz® (drospirenone), are the most effective hormonal options managing female acne given their synthetic anti-androgenic formulations.[54] Third-generation OCPs (Marvelon®, Mirvala®, Linessa®, Cyclen®, Tri-Cyclen®) are considered to be the least intrinsically androgenic, and are also thought to be effective in treating acne.[54] Importantly, first (Lolo®) and second (Min-Ovral®, Seasonique®, Indayo®, Alesse®, Aviane®, Alysena®, Triguilar®) generation OCPs have marked and varying androgenic effects, potentially worsening, triggering, or improving acne.[54] Other forms of hormonal contraception, such as Depo-Provera® and progesterone-only pills (Micronor® and Movisse®), which contain first-generation progestins, medroxyprogesterone acetate, and norethrindrone, or hormonal intrauterine devices (IUDs) that contain levonorgestrel without estrogen, may cause or exacerbate acne.[54] While progestin-only contraception is not advised for patients with acne-prone skin, Slynd®, a new and highly effective progesterone-only OCP, has shown promise for patients with acne-prone skin given the pathophysiology of drospirenone.[54] Importantly, patients should be advised that regardless of the hormonal contraceptive chosen, the effect on their acne may only be observed in 4–6 months. **Table 3** summarizes hormonal contraceptives and their impact on acne.

Can Treat Acne	Can Worsen Acne
Diane®-35	Lolo®
Yasmin®	Min-Ovral®
Yaz®	Seasonique®
Marvelon®	Indayo®
Mirvala®	Alesse®
Linessa®	Aviane®
Cyclen®	Alysena®
Tri-Cyclen®	Triguilar®
	Depo-Provera®
	Micronor®
	Movisse®

Table 3. Hormonal Management of Acne Vulgaris; *courtesy of Santina Conte, MD and Monica K. Li, MD, FRCPC, FAAD.*

Besides hormonal contraceptives, spironolactone, a potassium-sparing diuretic with anti-androgenic properties, reduces sebum production and hyperkeratinization in acne-prone follicles.[58] Dermatologists have been prescribing spironolactone off-label for acne in women for over three decades, with doses ranging from 50 to 200 mg per day, with 50 and 100 mg per day being the most commonly used.[57,58] Treatment can be initiated at 50 mg daily and titrated as tolerated in 25 mg increments. Importantly, patients should be notified that irregular menstruation is observed in 15–30% of patients, which can be managed by the addition of a third- or fourth-generation OCP or a hormonal IUD, as described above. Laboratory monitoring is typically not required for healthy women under the age of 45.[59] Spironolactone is contraindicated in pregnancy or for those trying to become pregnant due to its anti-androgenic effects, which may affect sex differentiation of the male during embryogenesis.[60,61] Importantly, once AV control has been attained with spironolactone, the dose can be tapered. The longer-term maintenance goal is to use topical agents only.

Regarding topical therapies, clascoterone can be considered, as described above (see *Topical Therapies* section). Otherwise, dapsone 5% gel (Aczone®) has anti-inflammatory properties that allow it to treat a variety of inflammatory skin conditions, including AV.[62] Additionally, a randomized study comparing the efficacy of tazarotene monotherapy to combination therapy with tazarotene and dapsone reported that combination therapy was more effective for treating comedonal acne.[63]

Special Clinical Considerations – Acne in the Pregnant Patient

Treating AV in the pregnant patient adds a layer of complexity, given that several of the above-mentioned medications and topicals are teratogenic and/or have not been extensively studied in a pregnant population. Notably, topical azelaic acid and glycolic acid have been deemed safest to use in pregnancy, as well as topical BP.[64,65] Topical clindamycin has been deemed compatible with pregnancy outside of the first trimester.[65] Both topical and oral retinoid formulations are either contraindicated or used with caution due to the teratogenic nature of the class.[65-67] Regarding topical retinoids, while the amount of drug absorbed from the skin is very low, there are case reports in the literature describing birth defects consistent with retinoid embryopathy.[65]

Therapeutics in the Horizon

Minocycline 4% foam (Amzeeq®) and the fixed-dose combination of tretinoin 0.1% with BP 3% cream (Twyneo®) are both approved for the management of AV in the United States, and may be available in Canada within the next 1–2 years. Minocycline foam was formulated with the goal of minimizing absorption and toxicity. When applied once daily, it demonstrated significant improvements in both inflammatory and non-inflammatory lesions compared to vehicle.[68,69] Tretinoin and BP cream, in a microencapsulated formulation, has also been shown to significantly reduce inflammatory and non-inflammatory acne lesions, as well as improve Investigator Global Assessment ratings.[70]

Benzoyl Peroxide Controversy

Since March 2024, there has been a great deal of controversy regarding the use of BP-containing products. The FDA recently tested 95 products and found that six contained elevated levels of benzene.[71] Benzene is classified as carcinogenic to humans, with research proving a causal relationship between benzene and acute myeloid leukemia, amongst other hematologic malignancies.[72] Valisure, the independent lab who performed the testing, reported that these BP acne treatments can break down and generate high levels of the carcinogen benzene when stored at high temperatures, notably 37°C, 50°C, and 70°C, representing body heat, standard pharmaceutical stability conditions, and extreme environmental heat, respectively.[71,73] However, the study was not conducted under ambient conditions, as most individuals would not store their acne treatments in such high temperature environments. The American Academy of Dermatology has since released an official statement regarding best practices for storing and handling products with BP. They recommend storing the product at room temperature or cooler conditions (e.g., in the refrigerator, not in or near direct sunlight or heat), and discarding products that are old (over 3–6 months after opening), expired or heat-exposed.[71,74,75]

Conclusion

AV is the most common dermatological condition worldwide, affecting people across a broad age range. Given its highly variable clinical presentation, management plans should be tailored to each individual patient, taking into account the presence and severity of inflammatory or non-inflammatory lesions, scarring, and/or the extent of hormonal contribution. A growing array of topical and oral treatment modalities reinforces the importance of staying current with the latest, most effective, individualized treatment combinations. Successful treatment of the acne-prone patient involves long-term acne clearance and minimizing the impact of undesirable sequelae, including scarring and dyspigmentation.

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Clinical Spotlight for Primary Care: Five Things to Know About Women and Girls with Bleeding Disorders

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1. Heavy menstrual bleeding (HMB) may be the first sign of a bleeding disorder.

Although common, HMB is often an underrecognized symptom, and affects up to 39% of individuals diagnosed with a bleeding disorder.[1] Taking a structured medical history is key. Tools such as the Pictorial Blood Assessment Chart[2] and the Menorrhagia Screening Tool[3] can aid in identifying HMB. Screening for iron deficiency, even in the absence of anemia, is essential, as low iron can impact cognition, energy, and quality of life.[4]

2. Bleeding assessment tools (BATs) aid diagnosis but are not definitive.

BATs are useful for identifying individuals who may need further evaluation; however, a normal score does not exclude a bleeding disorder, particularly in those without surgical or obstetrical challenges or in those who have a positive family history.[5] The self-administered BAT (**https://letstalkperiod.ca/self-bat/**) can facilitate early detection. An abnormal score should prompt further clinical assessment.

3. Tranexamic acid is effective for HMB and compatible with hormonal therapy.

Tranexamic acid, an antifibrinolytic agent, is a first-line therapy for HMB. Despite common misconceptions about thrombotic risk, it is safe for use with combined hormonal contraceptives.[4] While it is contraindicated in cases of active thromboembolism, and should be used with caution in those with thrombotic risk factors or prior thrombosis, routine avoidance is unnecessary. Provider unfamiliarity, concerns about off-label use, and access barriers continue to limit its uptake.[4]

4. Routine coagulation tests cannot definitely exclude a bleeding disorder.

Routine tests—such as prothrombin time, activated partial thromboplastin time, fibrinogen levels, and von Willebrand factor levels—may yield normal results, necessitating specialized testing guided by a hemostasis expert. Hemostatic testing must be interpreted in the context of female physiology—pregnancy can elevate factor levels, and hormonal therapies may influence test outcomes.

5. Multidisciplinary care optimizes outcomes.

Effective management of HMB and pregnancy requires collaboration between hematology and obstetrics and gynecology. Both specialties contribute to diagnosis, bleeding risk assessment, and treatment planning. Coordinated care supports fertility planning, pregnancy management, and counselling on fetal bleeding risks, ensuring timely and effective treatment.

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Managing Gout in the Clinic: Pearls for Family Medicine Specialists

Shelly Dunne, MD

Gout is the most common form of inflammatory arthritis worldwide, often presenting diagnostic and management challenges. However, it can also be gratifying to treat, as successful treatment provides relief from an extremely painful arthritis, and proper preventive strategies can lead to a gout free future. We will begin with a case from my clinical practice.

Case

Meet Steve, a 49-year-old engineer with a 3-year history of gout, primarily affecting his left big toe. His medical history includes type 2 diabetes, hypertension (HTN), and obesity. He is currently taking metformin, telmisartan, hydrochlorothiazide, and he uses indomethacin as needed. There is a strong family history of gout—his father and brother are both affected. Steve was born in the Philippines, is a lifelong nonsmoker, and consumes beer, mostly on weekends, up to 12 per week. While his diet is generally healthy, he has a particular fondness for shellfish and red meat. He has become increasingly concerned because his gout attacks have grown more frequent and prolonged. His most recent attack lasted longer than previously and involved his knee and ankle as well as his big toe. Laboratory findings were normal apart from an elevated uric acid level of 531 µmol/L. Steve is seeking guidance on how to best manage his painful attacks, and importantly, how to prevent future attacks. He is particularly interested in dietary modifications and has expressed concern about potential side effects of the urate-lowering therapies (ULT).

Diagnosis	Characteristics
Bacterial cellulitis	Erythema over the surface of a joint can be confused for a gout flare-up; however, the joint is typically nontender without the presence of effusion
Basic calcium phosphate deposition disease	Milwaukee shoulder syndrome (rapidly progressing crystal arthropathy involving the shoulder and intra-articular deposition of hydroxyapatite crystals)
Calcium pyrophosphate dihydrate deposition disease ("pseudogout")	Calcium pyrophosphate dehydrate in fluid aspirate from joint
Osteoarthritis	Gradual typical onset, commonly in the hand, knee, hip, or first metatarsophalangeal joint
Psoriatic arthritis	Characteristic skin and nail changes
Reactive arthritis	Inflammatory polyarthritis in reaction to bacterial infection (commonly Chlamydia trachomatis genitourinary infections or gastrointestinal infections with Campylobacter, Salmonella, Shigella, or Yersinia)
Rheumatoid arthritis	Slow onset with symmetric joint involvement, commonly in hands
Sarcoidosis	Lofgren syndrome involving the ankles and erythema nodosum that can appear similar to gout; however, hilar adenopathy and lung involvement are not present in gout
Septic arthritis	Associated fever, elevated white blood cell count, elevated erythrocyte sedimentation rate

Table 1. Differential Diagnosis of Gout; *adapted from AFP: Gout: Rapid Evidence Review by Karl T. Clebak, MD; Ashley Morrison, MD; and Jason R. Croad, DO.*

Diagnosing Gout

Accurate diagnosis is key to effective gout management. When a patient presents with a red, hot, swollen big toe, chances are very high that gout is the correct diagnosis. While any joint can be involved, the ankle, foot, and knee are commonly affected sites. While joint aspiration and synovial fluid analysis for uric acid crystals remain the diagnostic gold standard, aspiration may not be necessary in patients with multiple risk factors and elevated serum uric acid. However, it is worth considering other diagnoses, specifically septic arthritis and other inflammatory arthritides (**Table 1**).

Risk Factors for Gout

Understanding the risk factors for gout is equally important. Steve, for example, illustrates several classic risk factors: male sex, type 2 diabetes, HTN, family history of gout, and a purine-rich diet. **Table 2** provides a more comprehensive list of risk factors.

Acute Flare Management: Treat the Acute Attack with the Safest Option Available

When treating an acute gout attack, the goal is to use the safest option available for the individual patient (**Table 3**). Nonsteroidal anti-inflammatory drugs (NSAIDs) are a good option in low risk patients without renal disease, HTN or a history of gastrointestinal ulcers. Indomethacin is traditionally considered highly effective, and in my clinical experience, it often delivers reliable results. For patients who cannot tolerate NSAIDs, colchicine is a reasonable alternative, especially when initiated early in the course of the attack. While several dosing regimens exist, I prefer to use 0.6 mg twice daily, as higher doses are well-known for causing gastrointestinal side effects such as severe diarrhea. Intra articular steroids are an excellent option when joint injection is feasible. For more widespread or stubborn attacks, or in cases where NSAIDs, colchicine, and injections are not suitable, oral prednisone is my go-to. I usually prescribe a short 5-day course of treatment, starting at 25 mg and reducing by 5 mg each day.

Risk Factors for Gout
Comorbidities
• Cardiovascular disease • Diabetes mellitus • Diuretic use (loop and thiazide) • Elevated triglyceride and cholesterol levels • Hyperuricemia • Menopause • Obesity • Renal disease, including renal insufficiency and chronic kidney disease
Demographic factors
• Certain ethnic groups, including indigenous Taiwanese, Pacific Islander, and New Zealand Maori • Living in high-income countries (specifically North America and western Europe) • Male sex (incidence 2 to 6 times higher than in females)
Dietary factors
• Alcohol consumption • Diet rich in meat • Diet rich in seafood • Fructose-rich food and drink consumption

Table 2. Risk Factors for Gout; *adapted from AFP: Gout: Rapid Evidence Review by Karl T. Clebak, MD; Ashley Morrison, MD; and Jason R. Croad, DO.*

Medication & Dosage	Dosing	Notes
NSAIDs (examples only) • Naproxen • Indomethacin • Celebrex	• 375–500 mg p.o. bid • 25–50 mg p.o. bid-tid • 200 mg p.o daily	Roughly 5–7 days until the acute attack subsides; Assuming no NSAID contraindication, variable dosing with lower doses preferred if effective
Colchicine	• 0.6mg p.o. bid-tid	Roughly 5–7 days until the acute attack subsides; Diarrhea a common side effect, so keep dosing to this lower dose regimen
Corticosteroids • Prednisone p.o. • Methylprednisolone (depomedrol) IM	• Prednisone 25mg po on day 1 and reduce by 5 mg per day to 0 • Methylprednisolone (depomedrol) 80mg IM	Intraarticular preferred if possible

Table 3. Acute management of gout; *courtesy of Shelly Dunne, MD.*

Medication	Mechanism of Action	Dosage
Allopurinol (first line option for all patients	Xanthine oxidase inhibitor	Start at ≤100 mg daily (or lower in ≥ stage 3 chronic kidney disease); dosages can be titrated to 800 mg daily
Febuxostat (Uloric)	Xanthine oxidase inhibitor	Start at ≤40 mg daily; maximum dosage is 80 mg

Table 4. Chronic management of gout using urate-lowering therapies; *adapted from AFP: Gout: Rapid Evidence Review by Karl T. Clebak, MD; Ashley Morrison, MD; and Jason R. Croad, DO.*

Initiating Urate-Lowering Therapy: Key Considerations

Allopurinol remains the first-line agent for ULT and should be considered in patients who experience frequent gout flares, defined as two or more per year, as well as those with tophi (nodules that form from a mass of uric acid crystals at the joints or in the soft tissues) or x-ray evidence of gouty erosions. However, in certain cases, such as after the first gout flare in patients with uric acid levels higher than 540 µmol/L, greater than stage 3 or greater chronic kidney disease, or a history of urolithiasis, early initiation of ULT may be appropriate. ULT is not recommended for asymptomatic hyperuricemia. Notably, recent guidelines now conditionally recommend starting ULT during an acute attack, rather than waiting for the episode to resolve. When initiating allopurinol, it is best to start with a low dose of 100 mg per day, especially in patients with chronic renal failure, as this has been shown to reduce the risk of allopurinol hypersensitivity syndrome. Prophylactic therapy with NSAIDS, colchicine, or low-dose prednisone is recommended during the first 3–6 months of ULT to prevent acute attacks triggered by urate mobilization.

The treatment goal is to reduce serum uric acid to 360 µmol/L or lower, with regular serum urate monitoring and dose adjustments as needed. Genetic screening for the *HLA B5801* allele is recommended in patients of Southeast Asian and African American descent, as this allele is more prevalent in these populations, which places them at an increased risk for severe hypersensitivity reactions to allopurinol (**Table 4**).

Role/Safety of Febuxostat

Febuxostat (Uloric) is a newer xanthine oxidase inhibitor that effectively lowers serum uric acid levels more rapidly than allopurinol. Earlier concerns about increased cardiovascular risk lead to a recommendation for it's use as a second-line agent after allopurinol. However, more recent evidence from the FAST trial has refuted these concerns, suggesting that febuxostat may be safer than initially believed. It remains a valid second-line option, though caution is still advised in patients with preexisting cardiovascular disease. When prescribing febuxostat, it is best to start at the lower dose of 40 mg/day. Ongoing studies are under way that may further inform its safety profile and could lead to updates in future guidelines (**Table 4**).

Lifestyle and Self-management

Patients should be encouraged to adopt lifestyle changes that support long-term gout control. Strategies such as achieving and maintaining a healthy weight, engaging in regular physical activity, and following a low purine diet (limiting intake of red meat, organ meats, shellfish, and sugary beverages). It is also important to reduce alcohol consumption, especially beer, and to avoid beverages sweetened with fructose or other added sugars.

Patient Education

It is important to help patients to understand that while dietary modifications can support gout management, they rarely are sufficient on their own to lower uric acid levels to target. Most patients will require ULT for effective long-term control. Emphasizing the chronic nature of gout is necessary. Patients should be encouraged to adhere consistently to their prescribed ULT regimen and to undergo regular monitoring of their serum uric acid levels to ensure treatment goals are being met.

When to Refer

Referral to rheumatology is appropriate for complex cases of gout, particularly those with refractory symptoms or severe comorbidities such as renal failure or poorly uncontrolled HTN. It is also advisable to consider referral in cases of diagnostic uncertainty or when a diagnostic joint aspiration is indicated for a joint that is difficult to access.

Follow-up: Back to Steve

After a thoughtful discussion regarding the potential side effects of allopurinol and the overall risks and benefits of treatment, Steve agreed to begin ULT. Before starting, he was given a laboratory requisition to test for the *HLA B5801* allele, which fortunately came back negative. He was then prescribed 100 mg of allopurinol daily, along with colchicine 0.6 mg twice daily as prophylaxis against acute attacks. Steve also received counselling on lifestyle modifications, particularly to reduce his intake of beer, shellfish, and red meat. A follow-up appointment was scheduled for 3 months later, with instructions to complete serum uric acid testing beforehand. The plan is to adjust the allopurinol dose if his uric acid level has not reached the target of 360 µmol/L by that time.

Conclusion

In summary, gout remains a common, yet challenging condition encountered in family practice. By applying these evidence-based tips, clinicians can significantly improve outcomes for patients living with gout in 2025.

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Update on Early Prenatal Screening in 2025

Ken Seethram, MD

Advances in prenatal screening over the last three decades have delivered methods which broadly focus on genetics, fetal well-being, and preeclampsia screening, offering early insights in pregnancy to enable better risk management and planning strategies.

Key Takeaways
• First trimester is the critical window for comprehensive screening.
• NIPT is powerful but should not replace ultrasound or PE screening.
• Combining tools improves detection and allows earlier intervention.
• Patients benefit most from integrated screening with same-day risk disclosure when possible.
• Don’t skip ultrasound even with normal NIPT — 1.1% of anomalies will be missed.
• Low-dose aspirin is proven to reduce preterm PE by 62% if started by 14 weeks.
• NIPT is not suitable for vanishing twins or triploidy.
• Screening tools are complementary, not interchangeable.

Background

Prenatal screening has undergone tremendous evolution over the past 100 years. In 1933, Penrose[1] was the first to identify the association between Trisomy 21 (Down syndrome) and advanced maternal age. The discovery of the human diploid chromosome number 46 by Tijo and Levanin in 1956,[2] along with the development of metaphase karyotyping, enabled the precise correlation of the Trisomy 21 genotype with its clinical phenotype. This breakthrough opened the possibility for diagnostic testing, leading to the deployment of procedures such as amniocentesis and chorionic villus sampling (CVS).

Moving from Diagnostics to Screening

Amniocentesis and CSV are referred to as invasive diagnostic tests, each carrying an estimated 1% risk of miscarriage. In the mid-1980's the introduction of double and triple marker screening enabled the possibility of triaging pregnancies for invasive testing. Triple marker screening also expanded the scope of screening goals beyond Trisomy 21, to include other abnormalities such as aneuploidy and neural tube defects. While double and triple marker screening offered improved performance over age-based screening alone, they were associated with high false positive rates, and results which were delayed until 18–20 weeks of gestation.

By the late 1980's, prenatal screening was beginning to expand from a singular emphasis for detecting Trisomy 21 to a broader one on general fetal wellness. As well, consumer interest was changing, which drove the demand for prenatal screening options available as early as possible in pregnancy.

Three Advancements of Prenatal Screening

There have been three major developments in prenatal screening since 1990. These include advances in early ultrasound techniques and the description of markers for aneuploidy, the introduction of non-invasive prenatal testing (NIPT), and the development of preeclampsia (PE) screening.

Ultrasound

The early 1990s marked the dawn of a new era in screening with the development of ultrasound as a driving tool for prenatal screening. Nuchal Translucency (NT), (**Figure 1**), first described by Kypros Nicolaides,[3] became an early screening tool between 11–14 weeks of gestation. It offered an improved detection rate (versus serum screening) and a lower number of screen-positive results. When NT measurement was combined with serum markers such as serum pregnancy associated plasma protein-A (PAPP-A), and human chorionic gonadotropin (hCG), the screening achieved detection rates of 85%, with a 5% screen-positive rate, all prior to prenatal week 14. Subsequently, the correlation with nasal bone (NB) assessment,[4] followed by the addition of ductus venosus (DV) flow evaluation brought the "First trimester screen (FTS)" detection rates to 96% with a 3% screen-positive rate.[5] In addition, the ultrasound examination provided the added benefit of identifying fetal defects involving the spine, brain, cardiac, gastrointestinal, bladder, and limbs. DV flow has been linked to a 6.9-fold increase in the risk of congenital heart disease.[6] As such, DV assessment provides a functional screening tool to identify fetuses at a risk of congenital heart defects. Contemporary FTS screening between 11–14 weeks now includes five key factors for risk assessment: NT, NB, DV, serum PAPP-A and serum beta hCG.

The Fetal Medicine Foundation maintains the largest database of NT, NB, and DV measurements. To address quality assurance, access to this database is restricted to individuals accredited by the Fetal Medicine Foundation.[7] These users can connect through a variety of software platforms which then generates the risk assessment profiles for each patient. This process supports effective counselling to determine risk levels and discussions about further diagnostic testing options when indicated.

Ultrasound has evolved a multifaceted approach to screening, including aneuploidy screening via markers, anatomy assessment, pregnancy dating, and cardiac evaluation. This approach has expanded the focus of screening toward a broader view of fetal health.

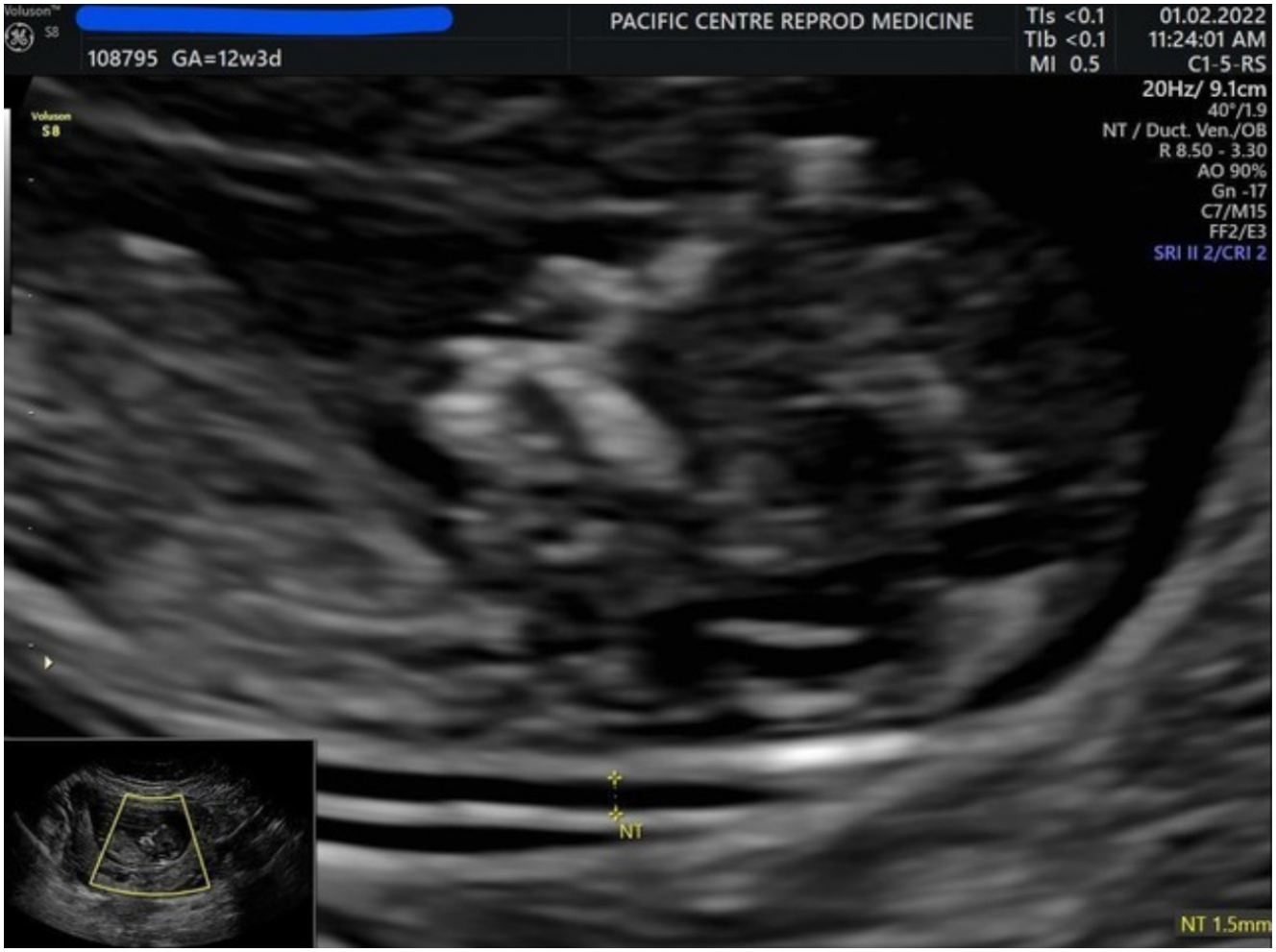

Figure 1. Nuchal translucency measurement at 12 weeks and 3 days of gestation; *courtesy of Ken Seethram, MD.*

Non-Invasive Prenatal Testing/Screening

Since 1997, it has been recognized that we can recover fragments of placental DNA[8] (small, typically under 1000 Kilo-base pairs) that can be detected in the maternal blood stream as early as 8 weeks of gestation. These fragments can be compared against the human genome library to reassemble the fetal genome and detect aneuploidies. Over time, various methods have emerged, including those targeting selective regions or individual mutations. Despite the expansion of some panels to include rare disease detection, the focus of NIPT remains the detection of aneuploidy.

NIPT aneuploidy (Trisomy 21, 13, 18) achieves detection rates higher than 99%. However, several notes and limitations prevent NIPT from serving as a standalone prenatal screening tool:

1. Approximately 1–3% of results yield a "no-call" or a "redraw request" often due to a low 'fetal fraction' (the proportion of placental versus maternal DNA), and can be linked with increased risks of aneuploidy, placental mosaicism, maternal malignancy, or technical issues. A redraw will yield a result in most cases.
2. Failed NIPT – options to consider include detailed anatomy ultrasound, genetic counseling referral including a discussion about invasive testing.
3. False positive rates remain below 1%.
4. NIPT is not applicable in cases of vanishing twins.
5. All NIPT methods (apart from SNP-based methods) do not detect triploidy.
6. Because NIPT analyzes placental cells, it may not reflect the current viability of the fetus.

Introduced in 2011, NIPT has since evolved to include screening for microdeletions and microduplications.[9] These types of mutations are quite rare but have broadened the scope and appeal of the test. In addition, the ability to determine fetal sex through NIPT has contributed to its growing popular appeal.

Pre-Eclampsia (PE) Screening

PE affects 2–8% of pregnancies and is a global contributor to 46,000 maternal deaths, and 500,000 fetal or newborn deaths. It is associated with primigravida status, multifetal pregnancy, obesity, and other medical conditions.[10] PE stems from imperfect implantation and placental development, wherein the lack of proper trophoblastic invasion and vascular recruitment lead to impaired placental bed perfusion. This compromised blood flow can manifest in fetal growth restriction and oligohydramnios during the second or third trimester. This impaired perfusion can then result in maternal physiological adaptations resulting in hypertension. In the short term, the hypertensive response is of benefit by improving placental perfusion. Over the longer term, the increase in maternal blood pressure can adversely affect end-organs, including the liver, bone marrow, and brain. Early detection of impaired placentation offers both clinical and therapeutic advantages, such as prompting closer surveillance, and timely initiation of low-dose Aspirin (ASA). The efficacy of ASA in reducing the risk of PE has been demonstrated in several trials. The 2017 ASPRE trial,[11] which used first trimester PE screening followed by randomized treatment with ASA versus placebo, demonstrated that administering 150 mg/day of ASA from 11–14 weeks until 36 weeks reduced the incidence of preterm preeclampsia by 62% in those at high risk of PE.

Early PE screening can consist of several elements including:

1. A detailed maternal history
2. Blood pressure measurements (two measures, simultaneously in both arms, repeated 5 minutes apart) to calculate the mean arterial pressure (MAP)
3. Uterine artery Doppler measurement
4. Serum proteins such as PAPP-A and Placental Growth Factor (PIGF)

Due to the accuracy and simplicity of screening, combined with the morbidity and mortality of PE, the International Federation of Gynecology and Obstetrics released a global initiative in 2019 to promote standardized PE screening strategies.[12]

Logistics of Early Testing

All of the early screening components described above can be completed prior to the end of the first trimester. The window for FTS screening is 11–14 weeks of gestation, (or a 45–84 mm of Crown rump length). Serum analytes used in PE screening can be processed using the same analyzer that processes chemical assays for beta hCG and PAPP-A. Several algorithms are available to support this integrated approach to screening:

1. NIPT alone. This can be performed as early as 8 gestational weeks.
2. NIPT combined with FTS. In this algorithm, venipuncture is performed prior to the FTS ultrasound. The serum is analyzed for biochemical markers, often within 35 minutes. This allows for an integrated risk assessment of markers with biochemistry, allowing for result disclosure immediately following the ultrasound. The plasma can also be used for NIPT, with turn-around-times ranging from 7–10 days depending on the provider. Alternately, patients may undergo a blood draw 7 days prior to the ultrasound, permitting a full disclosure of both FTS and NIPT results at the time of the ultrasound.
3. FTS with PE screening. This approach involves a combination of maternal history, sequential blood pressures, uterine artery Doppler assessment, and rapid analysis of placental growth factor. A results disclosure for both PE and FTS screening can be provided at the conclusion of the ultrasound visit.
4. A comprehensive approach that combines FTS with PE screening and NIPT.

Why Combine Screening Tools?[13]

NIPT reflects the genetic profile of placental DNA. Several studies have shown that approximately 5% of fetuses with low-risk NIPT had abnormal marker findings on first trimester ultrasound. As well, relying on low-risk NIPT results without ultrasound would miss approximately 1.1% of major structural anomalies. The inherent value of PE screening and the relative ease of adding it to FTS screening makes it a very appealing tool to help reduce downstream mortality and morbidity.

Patient Triaging Algorithm

Possible outcomes following early prenatal screening incorporating FTS, PE screening, and NIPT:

1. **Low-risk results across FTS, NIPT, and PE screening**
   a. These patients typically require prenatal care with minimal intervention.
2. **High risk findings on FTS or NIPT**
   a. These patients benefit from referral to Maternal Fetal Medicine for consideration of diagnostic testing such as CVS or amniocentesis.
3. **Abnormal DV flow:** if reversed DV flow is observed despite normal genetic assessment, fetal echocardiography is advised.
4. A **4-chamber cardiac view** is also recommended during the 11-14w scan.
5. **High Risk PE screening**
   a. These patients benefit from the administration of low-dose ASA (162 mg) nightly.
   b. As well, enhanced surveillance may include home BP monitoring, fetal growth surveillance, and other supportive measures.

Costs of Screening and Availability

In the Canadian health system, access to prenatal screening can vary across provinces and territories. At a minimum, patients should receive some form of risk assessment beyond maternal age to determine whether diagnostic procedures such as amniocentesis or CVS is advised. In the best-case scenario, comprehensive screening incorporates all available modalities. Many managed health systems have explored tiered screening, wherein an abnormal NIPT result is followed up with FTS screening, or vice versa, which offers effective screening at a low cost. However, a more integrated and thorough screening strategy in the first trimester may provide women with earlier, more complete information, and opportunities for downstream risk reduction. In this way, greater investments in early screening could provide reduced healthcare costs and improved outcomes later in pregnancy.

Summary

Over the last 30 years prenatal screening has undergone a remarkable evolution, enabling providers and their patients greater insight into fetal and maternal health. Advancements in genomics and NIPT, along with improvements in ultrasound markers, fetal anatomic assessment, and preeclampsia screening, have led to an unprecedented opportunity to provide more meaningful information early in pregnancy. These evolving tools offer an opportunity to change the way we provide prenatal care in the future.

Appendix: Summary Tables

1. Initial Time Window
All prenatal screening should ideally be completed before 14 weeks gestation. The optimal window is between 11–14 weeks, when the crown-rump length (CRL) measures between 45–84 mm.
2. Screening Options and What to Know
Option A: NIPT Alone
• Detects Trisomy 21, 18, and 13 with high sensitivity (>99%).
• May miss structural anomalies and is not useful in vanishing twins or triploidy.
• Best for patients who decline ultrasound but want early genetic screening.
Option B: NIPT + First Trimester Screening (FTS)
• Combines genetic risk data from NIPT with anatomic and functional screening from ultrasound and biochemistry.
• Ultrasound includes nuchal translucency (NT), nasal bone (NB), ductus venosus (DV) flow, and markers like PAPP-A and beta hCG.
• Allows immediate disclosure of results when bloodwork is pre-drawn.
• This is a preferred option for comprehensive early assessment.
Option C: FTS with Pre-Eclampsia (PE) Screening
• Adds risk prediction for preeclampsia using maternal history, blood pressures (both arms, repeated), uterine artery Doppler, and placental markers (PAPP-A and PlGF).
• Enables timely initiation of low-dose aspirin (162 mg at bedtime) for high-risk patients, which has been shown to reduce preterm preeclampsia by up to 62%.
Option D: Full Integration (Best Practice)
• Combines NIPT, FTS, and PE screening.
• Offers the most complete picture of fetal and maternal risk early in pregnancy.
• Can often be done in a single visit with appropriate timing and logistics.
3. What to Do with Results
• If all results are low-risk (FTS, NIPT, and PE), continue with routine prenatal care.
• If there are high-risk findings on NIPT or FTS, refer to Maternal-Fetal Medicine for consideration of diagnostic testing like CVS or amniocentesis.
• If ductus venosus flow is abnormal (e.g., reversed flow), recommend fetal echocardiography, even if genetic tests are normal.
• If PE screening shows high risk, start ASA 162 mg nightly and consider enhanced surveillance including home blood pressure monitoring and serial fetal growth assessments.

Screening Modalities Overview

Screening Modality	Timing	Purpose	Who Should Get It
FTS (Ultrasound + Biochemistry)	11–14 weeks	Trisomy screening, structural anomalies, cardiac defects	All patients; baseline screen
NIPT (cfDNA blood test)	As early as 8 weeks	High sensitivity screen for trisomy 21/18/13, fetal sex	All patients, esp. maternal age >35, prior aneuploidy, or high-risk ultrasound
PE Screening (BP, Doppler, PAPP-A, PIGF)	11–14 weeks	Predict preeclampsia; ID high-risk for aspirin	All patients, especially primigravida, obesity, twins, or medical comorbidities

Results and Recommended Actions

Result	Recommended Action
Low-risk FTS, NIPT, PE	Continue routine prenatal care
High-risk NIPT or FTS	Refer to Maternal-Fetal Medicine; consider CVS or amniocentesis
Abnormal ductus venosus flow (e.g., reversed flow)	Recommend fetal echocardiogram
High-risk PE screen	Start ASA 162 mg nightly, monitor BP, fetal growth surveillance

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Financial Disclosures

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