Journal of Gynecology and Obstetrics
2020; 8(6): 195-210
http://www.sciencepublishinggroup.com/j/jgo
doi: 10.11648/j.jgo.20200806.18
ISSN: 2376-7812 (Print); ISSN: 2376-7820(Online)

Consensus on Management of Dermatophytosis and Vulvovaginal Infections in Non- Pregnant and Pregnant Females

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To cite this article:

Sanjiv Kandhari, Piyush Prabhat, Madhu Rengarajan, Sunil Dogra, Chitra Nayak, Dibyendu Banerjee, Jayashree Sridhar, Mukesh Patil, Neena Singh, Pondicherry Gopinath, Ratna Talukdar, Vishalakshi Viswanath. Consensus on Management of Dermatophytosis and Vulvovaginal Infections in Non- Pregnant and Pregnant Females. *Journal of Gynecology and Obstetrics*. Vol. 8, No. 6, 2020, pp. 195-210. doi: 10.11648/j.jgo.20200806.18

Received: November 11, 2020; **Accepted**: November 25, 2020; **Published**: December 16, 2020

Abstract: There has been an increasing prevalence of dermatophytosis among the females in India, over the last 5-6 years. Similarly an increase in the occurrence of vulvovaginal infections has also been observed. The recommendations from existing guidelines do not focus on these infections in females and provide optimal outcomes in real world setting. Hence, the aim of the present consensus was to formulate recommendations based on current clinical experience to address these infections. A multispecialty panel of 12 members consisting of 7 gynecologists and 5 dermatologists participated in the pursuit of obtaining consensus by modified Delphi process. All the panelists formulated questionnaire after critical review of literature. Four rounds of questionnaires containing a total of 63 questions were floated through Google docs survey and responses were marked by all the panelists. Agreement for a given question/statement as ≥75% was set to achieve consensus. Out of the 63 questions/statements, consensus was obtained on diagnosis and treatment of dermatophytosis and VVI in non-pregnant and pregnant females, in 61 statements. The panel also formulated treatment algorithm for dermatophytosis and VVI. The present consensus will provide a guidance to the clinicians in India regarding management of dermatophytosis and VVI in pregnant and non-pregnant females in the current scenario of therapeutic challenges in both the infections.

Keywords: Dermatophytosis, Vulvovaginal Infections, Consensus, Pregnancy, Non-pregnant Females

1. Introduction

Superficial fungal infections are caused by dermatophytes, non-dermatophytic moulds and commensal yeasts such as *Candida albicans and Malassezia* species [1]. There is an increase in the prevalence of dermatophytosis, the most common superficial mycoses, in India and other tropical countries [2]. Patients more often tend to present with chronic, recurrent, steroid modified, extensive lesions which lead to disfigurement, loss of workplace productivity and thus impose socio-economic burden on the society [3-5].

Verma et al. mentioned that there is a rise in prevalence of tinea corporis et-cruris, not only among women who are overweight, but also in slim women in the recent years. They cited the change in the fashion trend of wearing tight fitting clothes like jeggings and leggings which are not suitable for our hot and humid climate to be the reason for this increased frequency of infections. Tight fitting garments lead to friction and maceration of the skin owing to sweating, further resulting in increased predisposition to dermatophytosis [6].

Involvement of genital skin by dermatophytes in women is less documented as compared to males. Pubic area is particularly more involved and history of trimming pubic hair or application of topical corticosteroid containing fixed dose combination should be elicited in these patients [7]. It is seen in clinical practice that topical corticosteroids (TCS) are commonly misused for treatment of cutaneous inflammatory dermatophytosis. However, the temporary reduction in inflammation by TCS leads to incomplete clearance of the fungi, ultimately leading to chronicity of the infection and extensive involvement [6].

Similar trend has been observed in cases of vulvovaginal infections (VVI) wherein, increased prevalence of *Non-albicans Candida (NAC)* has been reported. This may be attributed to misuse of the over-the-counter (OTC) antifungal corticosteroid combination creams, which has led to increased MICs of commonly used antifungal drugs against dermatophytes and *Candida* and thus reduced clinical cure rate and increased recurrence [8, 9].

Quite often, female patients with dermatophytosis of the intimate areas tend to consult the gynecologists. Apart from the recently published Indian consensus on management of dermatophytosis by Rajagopalan et al (ECTODERM) [10], there are no current Indian guidelines which address the issues in management of dermatophytosis and VVI in pregnant and non-pregnant women. In the above consensus, pregnancy had been included as a special population group.

Therefore, the present consensus was planned to obtain recommendations for management of dermatophytosis of the glabrous skin (excluding isolated nails and hair involvement) and VVI in pregnant as well as non-pregnant women.

2. Scope and Objective

Management of dermatophytosis and VVI has become complex with the need for research and understanding gaps that have to be addressed to provide superior patient care. The scope of this consensus is to meet this gap and provide a national update on the diagnosis and management of these infections in women.

The primary objective of this evidence and opinion-based consensus is development of empirical and definitive treatment recommendations appropriate for dermatophytosis of the glabrous skin especially tinea corporis, tinea cruris and VVI keeping in mind the practical considerations in India (changing trends, climate, patient's attitude, affordability and social factors). The secondary objective is the implementation of recent knowledge relating to diagnosis and the treatment of dermatophytosis and VVI.

3. Methodology

Quite often, females with tinea cruris et-corporis tend to consult gynecologists. Hence, a multispecialty panel of 5 dermatologists and 7 gynecologists with vast experience in the treatment of dermatophytosis and VVI from different parts of India was selected. Targeted invitations were sent to these experts for participation in the development of consensus.

The guideline development followed a structured and pre-defined process. A series of presentations were made, followed by in-depth discussions in an open forum in the first meeting held in July 2019. Recommendations for clinical practice were formally consented, explicitly considering all relevant aspects namely diagnosis of dermatophytosis and VVI, management of these infections in pregnant and non-pregnant females via 4 rounds of web based modified Delphi method with a total of 63 questions. Consensus recommendations were proposed based on the available evidence, and expert opinions [Table 1] [11]. The final document was discussed in second meeting held in October 2019 moderated by a facilitator with participation of the entire group. A statement was regarded as consensus when agreement was achieved by 75% or more of the experts according to the modified Delphi procedure.

The present consensus was done in accordance with ethical guidelines of latest amended Helsinki's declaration. The methodology adopted for the present research work does not require ethics committee approval and informed consent for participation. Flowchart of consensus is depicted in figure 1.

Table 1. *Strength of recommendations and quality of evidence [adapted from Soman R et al] [11].*

Strength of recommendation	Description
Grade A	Panel strongly recommends the concerned statement
Grade B	Panel moderately recommends the concerned statement
Grade C	Panel weakly recommends the concerned statement

Strength of recommendation	Description
Level of evidence	**Description**
Level 1	At least one related randomized clinical trial/systematic review/meta-analysis
Level 2	Evidence from non-randomized clinical trial, multicentric observational/analytical studies, multiple time series.
Level 3	Evidence from expert committee opinions, case series, clinical authority recommendations.

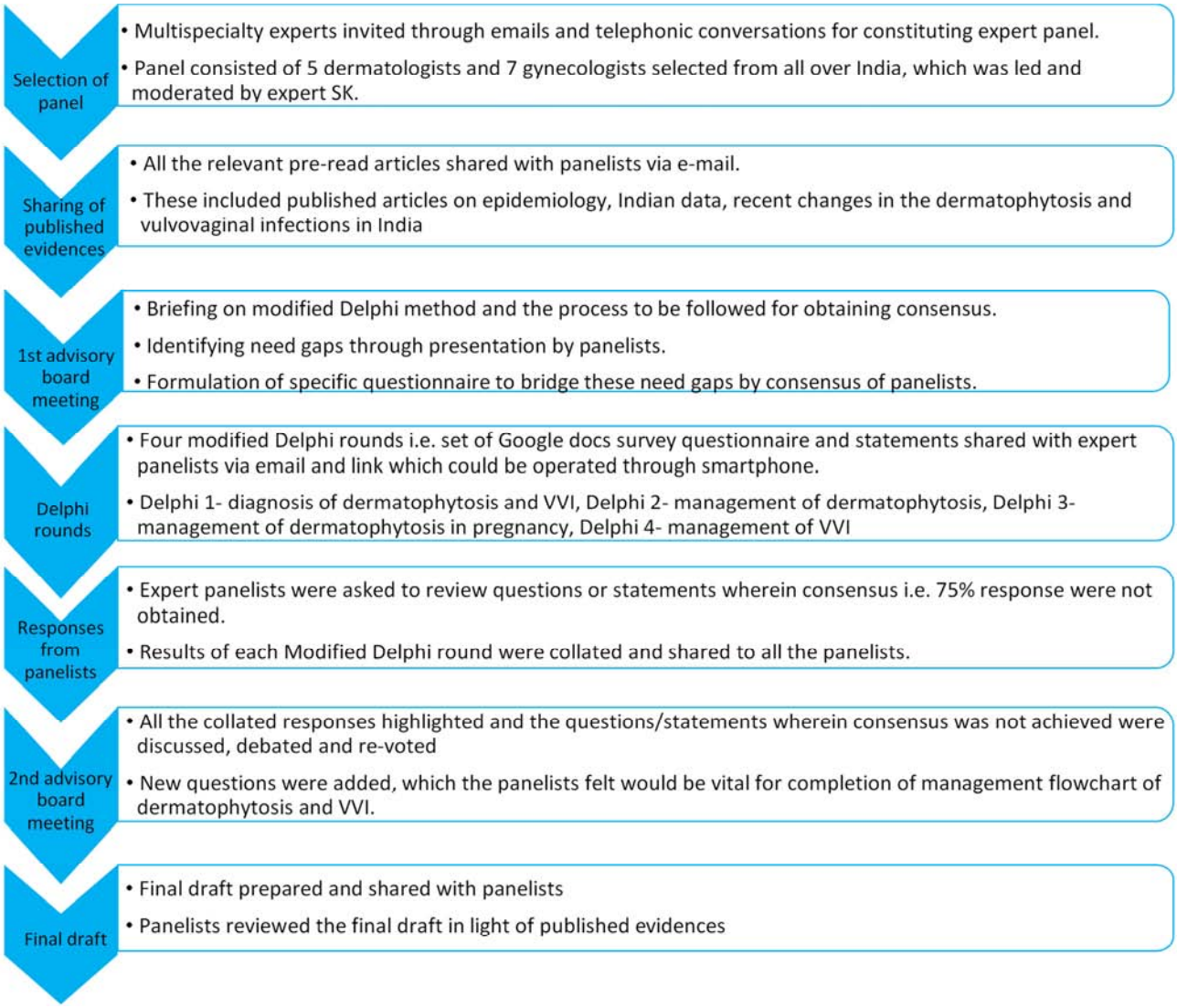

Figure 1. *Workflow of the present consensus through modified Delphi method.*

4. Background

Definition

Definitions agreed upon unanimously by the subject experts is given in Table 2. [Adapted from Rajagopalan et al, Lema et al, CDC 2015 sexually transmitted diseases treatment guidelines and Wilson J] [10, 12-14].

Table 2. *Definitions related to dermatophytosis and vulvovaginal infections [Adapted from Rajagopalan et al, Lema et al, CDC 2015 sexually transmitted diseases treatment guidelines, Wilson J] [10, 12- 14].*

Term	Definition
Dermatophytosis	Dermatophytosis (ringworm or tinea) is an infection of skin or skin derivatives caused by fungi known as dermatophytes leading to erythema, small papular vesicles, and scaling. Dermatophytes are filamentous fungi prone to invade and multiply in keratinized tissue i.e. skin, hair and nails.
Chronic Dermatophytosis	Dermatophytosis is considered to be chronic when the patients have suffered from the disease for more than 6 months to 1 year duration, with or without recurrence, in spite of being treated.
Recurrent Dermatophytosis	Dermatophytosis is considered to be recurrent when there is re-occurrence of the infection within few weeks (< 6 weeks) after completion of treatment.

Term	Definition
Relapse:	Relapse denotes the occurrence of dermatophytosis, after a longer period of infection free interval (6-8 weeks) in a patient who has been cured.
Recalcitrant	Recalcitrant dermatophytosis refers to the presence of persistence of lesions with no cure or partial cure in spite of use of antifungals in the appropriate dose and duration.
Tinea incognito	Tinea incognito is modified/ atypical clinical presentation of dermatophytic infections which are essentially preceded by improper use of topical/ systemic corticosteroids, immunosuppressant like calcineurin inhibitors etc.
Uncomplicated VVC	Uncomplicated VVC includes sporadic, infrequent, mild to moderate cases, occurring in most non-immunocompromised patients, most likely due to *Candida albicans*.
Complicated VVC	Complicated VVC includes recurrent, severe cases, occurring mostly in immunocompromised, diabetic patients and usually due to non-albicans *Candida* (NAC).
Recurrent VVC	Recurrent VVC is defined as four or more episodes of VVC in one year.
Recurrent BV	Recurrent BV is defined as one or more episode within 1 year of successful treatment.

5. Results

Overall, consensus recommendations were achieved in 61 statements based on responses of Delphi rounds, detailed discussion, and published literature related to the statements. Out of these, 52 statement recommendations were obtained through four rounds of modified Delphi process. In order to cover the unattended lacunae in the therapy of dermatophytosis and VVI, panel members unanimously decided to include 11 statements during the 2nd advisory board meeting, which would positively impact the management of above stated infections and improve the cure rates. These statements were subjected to modified Delphi process. All the recommendations including the quality of evidence/ literature and strength of recommendation are depicted concisely in table 3.

Table 3. *Results of Delphi rounds.*

Sr. No	Statement	SoR & LoE
	DIAGNOSIS OF TINEA INFECTIONS	
1	Tinea infections are mainly diagnosed clinically, but in selected cases where clinical diagnosis is difficult, laboratory diagnosis should be opted.	A3
2	Preference for point of care testing for dermatophyte infections is 10% KOH test.	A1
3	Sample should be collected from margins of the lesion using dermal blunt curette in patients with recalcitrant infection.	B1
4	Preference for doing culture in dermatophytic infections is multiple sites of involvement, presence of inflammatory lesions.	C2
	DIAGNOSIS OF VVI	
5	Vulvovaginal infections (VVI) is routinely diagnosed clinically with laboratory diagnosis being used in selected cases when clinical diagnosis is difficult.	A3
6	Wet mount test should be done in mixed infections, since it can differentiate between all causes of vaginitis.	A2
7	Whiff test can be used to diagnose bacterial vaginosis (BV) wherein clear cut clinical diagnosis is not possible.	B2
8	In mixed infections, simple pH strip test can be used to diagnose VVC.	B3
9	Fungal culture should be done at least in complicated VVC to identify the species of *Candida*, as this will help to optimize therapy.	A1
	TREATMENT OF NAÏVE TINEA	
10	Initiation of treatment in patient with localized (≤ 5cm) naïve (new) tinea infection should be with topical antifungal therapy alone.	A1
11	Newer azole class of antifungals or terbinafine are preferred topical therapy in localized and extensive (≥ 5cm, multiple/ widespread lesions, multiple sites of involvement) naïve tinea infection.	B2
12	Ideal duration of topical therapy in treatment of localized and extensive naïve tinea infection should be of minimum 4 and 6 weeks, respectively.	A1
13	In naïve tinea infection, combination (topical + systemic) therapy is indicated in extensive involvement, less/ no response / poor patient compliance to topical therapy and difficult to treat cases.	A1
14	Terbinafine and itraconazole can be effective choices of systemic therapy in treatment of naïve tinea infection, but itraconazole 200 mg/day is preferred.	C2
15	Ideal duration of systemic therapy in treatment of extensive naïve tinea infection should be of minimum 4 weeks	A3
16	Topical antifungal drug should be applied inwards from 2 cm beyond the margins of the lesion and over the lesion for at least 2 weeks after complete clinical resolution.	A3
	TREATMENT OF RECALCITRANT TINEA	
17	Initiation of treatment in patient with localized recalcitrant tinea infection should be done with 2 topical antifungals, preferably of different class and combination therapy of topical and systemic antifungals in extensive recalcitrant cases.	B2
18	Newer azoles like luliconazole, sertaconazole, eberconazole or terbinafine are preferred for topical therapy in recalcitrant tinea infection.	B3
19	Ideal duration of topical therapy in the treatment of localized and extensive recalcitrant tinea infection should be 6 weeks and ≥6 weeks, respectively.	A3
20	Terbinafine and itraconazole can be effective choices of systemic therapy in treatment of recalcitrant tinea infection, but itraconazole 200mg/day is preferred.	A1
21	Duration of systemic antifungal therapy in treatment of localized (not responding to 2 topical antifungals) and extensive recalcitrant tinea infection should be 4 and >6 weeks, respectively provided that liver function test done at 4th week is normal (itraconazole/terbinafine).	A3

Sr. No	Statement	SoR & LoE
22	If there is no/ less response to 1st line systemic drug of combination therapy of recalcitrant tinea cruris/corporis following treatment for adequate duration and ensuring compliance, then systemic antifungal should be continued for ≥ 6 weeks/change of systemic antifungal if liver function are normal at 4 weeks (itraconazole/terbinafine) and replacement of 1st topical with other topical of different class should be done.	A2
23	Low dose of antifungal prescribed for long duration or high dose prescribed for short duration should be strictly avoided as it may contribute to reduced response to these drugs.	B3
	TINEA INCOGNITO/ STEROID MODIFIED TINEA	
24	In tinea incognito, oral antifungal therapy should be continued in combination with topical antifungal drug, but topical corticosteroid should be stopped immediately.	C1
25	Itraconazole 200 mg/day> terbinafine 500 mg/day (250 mg twice a day) is preferred systemic therapy in tinea incognito.	B2
26	Azoles and other topical antifungals with significant anti-inflammatory action like sertaconazole, eberconazole, ciclopiroxolamine; luliconazole with reservoir effect and wide spectrum of action dermatophytes, especially *Trichophyton mentagrophytes* should be preferred for topical therapy of tinea incognito.	A3
	ANTIFUNGAL + TOPICAL CORTICOSTEROID (TCS)	
27	Topical corticosteroid (all classes) therapy either alone or as combination cream should be strictly avoided in the treatment of any type of dermatophytosis	A2
	SUPPLEMENTAL THERAPY	
28	Salicylic acid 3% can be used along with antifungal drugs as a part of initiation therapy in recalcitrant infection, but its use should be avoided in flexures and face due to irritation potential.	C3
29	Oral antihistamines can be used in management of tinea infections	B2
30	Moisturizers with barrier repair can be used in management of tinea infections	B3
31	Starch free medicated powder/talc may be used in obese patients with tinea cruris, since it will help to keep the area dry.	B2
	MANAGEMENT OF TINEA CORPORIS ET CRURIS IN PREGNANCY & LACTATION	
32	As compared to non-pregnant state, tinea infections in pregnancy may be more inflammatory, widespread, with multiple sites of involvement.	A2
33	Initiation of treatment in tinea infection in pregnancy should be with topical antifungal therapy alone	A2
34	Terbinafine and ciclopiroxolamine are preferred for topical therapy.	B2
35	Ideal duration of topical therapy in treatment of naïve and recalcitrant tinea infection in pregnancy should be of minimum 4 and 6 weeks, respectively.	B3
	MANAGEMENT OF VULVOVAGINAL INFECTIONS (VVI) IN NON-PREGNANT PATIENTS	
36	Initiation of treatment of uncomplicated VVI should be done with intravaginal antifungal therapy alone.	A1
37	Preferred intravaginal formulation of antifungal drug in treatment of VVC/ mixed VVI	No consensus
38	Fenticonazole is preferred, followed by clotrimazole as choice of intra-vaginal therapy of VVC, including cases not responding to fluconazole.	A2
39	Optimal duration of intravaginal therapy in uncomplicated VVC is 1 day for fenticonazole/ 6 days for clotrimazole.	A3
40	Itraconazole is the preferred systemic antifungal drug in treatment of VVC	A2
41	Optimal duration of therapy with itraconazole in uncomplicated VVC should be 200 mg BID for 1 day.	A1
42	Initiation of treatment of complicated VVI should be done with intravaginal + oral therapy.	A3
43	Optimal duration of intra-vaginal therapy in complicated VVC is 2 days for fenticonazole, 6 days for clotrimazole.	A2
44	Most effective regimen of fenticonazole therapy in complicated VVC is day 1 + day 3 regimen.	A3
45	Optimal duration of therapy with itraconazole in complicated VVC should be 200 mg/day for 7 days	A3
46	Fenticonazole, clotrimazole + clindamycin are preferred intra-vaginal drugs for treatment of mixed VVI.	A2
47	Optimal duration of intra-vaginal therapy in mixed VVI is 2 days for fenticonazole/ 6 days for clotrimazole + clindamycin.	A2
48	Dose and duration of therapy needs to be increased in complicated VVI.	B2
49	In case of less/no response to conventional drugs, intravaginal boric acid/ liposomal amphotericin B can be used, for treatment of VVC	C3
50	Metronidazole 0.75% gel is preferred for intra-vaginal therapy in bacterial vaginosis (BV).	B3
51	Oral therapy in BV is indicated in selected patients with no/ less response/ poor compliance to intravaginal therapy, recurrent BV.	A2
52	Oral metronidazole 500 mg BID x 7 days is preferred over clindamycin 300 mg BID x 7 days or Tinidazole 1 gm OD x 5days for treatment of recurrent bacterial vaginosis (BV).	A2
	MANAGEMENT OF VULVOVAGINAL INFECTIONS (VVI) IN PREGNANT PATIENTS	
53	Treatment of VVI in pregnancy is initiated with intravaginal therapy only	A3
54	Fenticonazole is preferred for intra-vaginal therapy of VVC, mixed VVI.	A2
55	Dosage of intravaginal fenticonazole for management of VVC, mixed VVI in pregnancy is day 1 and day 3	A2
56	Metronidazole 0.75% gel are preferred for intra-vaginal therapy of bacterial vaginosis (BV).	B2
57	Systemic antifungals should be avoided in the treatment of VVC/ mixed vaginitis.	B1
58	Systemic metronidazole can be used in recurrent BV; less/no response/ poor compliance to intravaginal monotherapy from 2nd trimester, while its use should be strictly avoided in 1st trimester.	A2
	GENERAL MANAGEMENT OF VVI	
59	Vaginal probiotics can be given to reduce relapse in VVI	A1
60	Probiotics along with core therapy helps to improve cure rate in VVI.	No consensus
61	Optimal duration of systemic probiotic therapy in management of VVI should be 1 month	B2
62	Routine use of intimate wash helps to reduce the recurrence/relapse after completion of main therapy for VVI	C2
63	Treatment of male partner is recommended in VVI, as they are carriers of the pathogens.	B2

Where SoR is strength of recommendation, LoE is level of evidence.

6. Discussion

As stated earlier, female patients visit the gynecologists frequently for treatment of infections of intimate areas. In actual clinical practice, though gynecologists may not encounter these dermatophytic infections as frequently as VVI, still they form significant bulk of patients. Therefore, it becomes imperative that management recommendations of tinea infections be laid down for gynecologists. Also, there are no recent Indian guidelines for the management of VVI and the recommendations given in western guidelines are not practically applicable in Indian settings. The present consensus was planned in order to bridge these need gaps in management of tinea infections and VVI in pregnant and non-pregnant females.

6.1. Dermatophytosis

6.1.1. Diagnosis

General consensus of the panelists was that although, dermatophytosis is mainly a clinical diagnosis, given the current changes in clinical presentation of tinea infections in India, it becomes vital to opt for laboratory diagnosis prior to start of the treatment in case of diagnostic difficulty. Quality, along with quantity of sample plays a major role in accurate diagnosis of tinea infection [15, 16]. Panelists concurred that the sample should be preferably taken by scraping from the margins of the lesion with a dermal blunt curette, which was in corroboration with recommendation from recently published consensus by Rajagopalan et al [10].

Point of care testing should be done by 10% potassium hydroxide (KOH) wet mount, as it is comparatively simple, economically feasible, and rapidly done [10]. It was agreed upon that KOH wet mount could be done in patients with recalcitrant dermatophytosis. General consensus with regard to fungal culture was that it could be done in selected patients with multiple sites of involvement and inflammatory lesions when feasible.

6.1.2. Management of Dermatophytosis in Non-pregnant

i. Optimal Choice of Antifungal Drug

Dermatophytes are keratinophilic and are usually confined to epidermal layers that are rich in keratin, which they feed on [17]. Due to this reason, treatment of localized naïve tinea lesions (≤5cm) by topical antifungal drugs is usually sufficient by virtue of the high local concentration achieved [18], which is in accordance with the recommendations made by panelists. Various topical antifungals that are commercially available are azoles, allylamines, morpholene and ciclopiroxolamine.

It has been reported that azoles have good efficacy in terms of clinical as well as mycological cure [19]. Azoles can be particularly more favorable, owing to their anti-inflammatory action, broad spectrum of antifungal coverage and additional antibacterial action [20]. Newer azoles like luliconazole have advantages such as higher fungicidal action against *Trichophyton* species, once daily dosing (thus better patient compliance), high concentration in the stratum corneum and higher skin retention time [21]. Sertaconazole is reported to have better anti-inflammatory and antipruritic action as compared to other topical antifungals [22]. Eberconazole has been shown to possess anti-inflammatory action comparable to aspirin and ketoprofen with additional activity against gram positive bacteria [23]. Similarly, fenticonazole also possesses additional antibacterial action against certain gram positive bacteria like *Staphylococcus*, *Streptococcus* and therefore can be used in dermatophytosis with secondary bacterial infection [24]. Topical antifungal agent with different mechanism of action such as ciclopiroxolamine, amorolfine can be effective whenever there is concern of reduced efficacy of conventional topical antifungals [20, 25]. Ciclopiroxolamine has been shown to possess significant anti-inflammatory action, which was more than that of 2.5% hydrocortisone [26]. However, panelists gave the consensus in favor of use of newer azoles like luliconazole, sertaconazole, eberconazole or terbinafine in local as well as extensive (>5cm, multiple lesions/ widespread/ multiple sites involvement) naïve and recalcitrant tinea infections.

In patients with recalcitrant dermatophytosis and extensive lesions, combination therapy of systemic and topical antifungal drugs is recommended [17, 20, 27, 28]. In addition to these, consensus was in favor of use of this combination therapy in patients with difficult to treat tinea, poor compliance to topical therapy and failure/ reduced response to topical therapy. As per Delphi results, initiation of treatment of localized recalcitrant lesions should be with 2 topical antifungals, preferably of different class and that of extensive recalcitrant tinea cruris and corporis with combination therapy of systemic and topical antifungal drugs. In addition salicylic acid 3% was also recommended by the experts, as a part of initiation therapy in recalcitrant dermatophytosis. Since dermatophytes are keratinophilic and localized mainly in stratum corneum, removing superficial layers of the skin helps to remove the fungus, therefore better cure rates can be anticipated. This was proven in a clinical study, wherein salicylic acid was used in recalcitrant dermatophytosis and clinical and mycological cure rate of 88% was obtained [29]. However, it should be noted that salicylic acid has significant potential to cause burning sensation and irritation in sensitive areas (flexures like groin, and inframammary area, face, axilla and genitals etc.) and when applied to inflammatory lesions of dermatophytosis [29].

According to the panelists, terbinafine and itraconazole are the effective choices of systemic therapy in both, naïve as well as recalcitrant tinea cruris and corporis, but itraconazole is preferred.

ii. Dose and Duration

It is cited in literature that topical therapy should be given for 4-6 weeks. In case of naïve tinea infection, minimum duration of topical therapy should be 4 weeks, while that in recalcitrant cases should be ≥ 6 weeks [10]. As per Delphi

responses, general consensus was that duration of topical therapy should be at least 4 weeks in case of localized naïve cases, 6 weeks in case of extensive naïve lesions and localized recalcitrant tinea lesions and > 6 weeks in case of extensive recalcitrant lesions. It is known that dermatophytes spread centrifugally i.e. away from the center of the lesion owing to central clearance by cell mediated immunity. As per literature, topical antifungal drug should be applied inward from 2 cm beyond the margin of the lesion and over the lesion, for at least 2 weeks after complete resolution of symptoms, which is termed as "Rule of two" [6]. This was in accordance with the consensus of the panelists.

ECTODERM by Rajagopalan et al states that in case of systemic drugs, duration of therapy should be 2-4 weeks in case of extensive naïve tinea infection and ≥4 weeks in recalcitrant cases, provided that liver function tests done at the end of 4 weeks are normal [10]. This is due to the fact that systemic antifungals are known to cause hepatotoxicity with continued usage. Recommendations of the panelists was in favor of 4 weeks systemic therapy in extensive naïve and localized recalcitrant infection with non-response to 2 topical antifungals and ≥6 week therapy in extensive recalcitrant lesions, if the liver function tests are normal after 4 weeks of therapy. As per Delphi results, recommended dose of itraconazole was 200 mg/day and that of terbinafine was 250 mg/day in naïve dermatophytosis. This was in accordance with recommendations of previously published consensus on management of dermatophytosis [10]. Panelists opined that prescribing antifungal drugs in low dose for longer duration or high dose for short duration should be strictly avoided since both the regimens contribute to reduced response to these drugs.

iii. No/less Response to 1st Line Therapy

There are multiple reasons for less/ no response to 1st line antifungal drug therapy. These include incomplete duration of therapy, inadequate dose, inappropriate selection of antifungal drugs, poor compliance, mycological and clinical resistance and persistence of predisposing factors like poor hygiene, sharing of fomites, wearing of synthetic tight garments, obesity etc. [30, 31]. Clinical resistance cannot be predicted, but it highlights the importance of selection of antifungal therapy tailoring to the clinical needs of the patients [32]. Emergence of *Trichophyton mentagrophytes* as the commonest culprit in tinea infections in India, is reported to be another major cause for such low therapeutic response by some authors. Low or clinical non – response in patients infected by *T. mentagrophytes* has been considered to be due to the presence of more inflammatory and extensive lesions which are less responsive to conventional dose and duration of usual antifungal drugs [3, 33]. Experts agreed that whenever there is reduced/ no response to 1st line therapy following treatment for adequate duration and ensuring compliance, then replacement of topical antifungal with another topical drug of other class and continuation of 1st line oral antifungal drug for more duration/change of systemic antifungal drug, if liver function test at 4 weeks is normal (for itraconazole/ terbinafine), may be considered.

iv. Tinea Incognito / Steroid Modified Tinea

Main issues with use of topical corticosteroids in India are the unchecked availability of these creams either as isolated or in combination as over the counter (OTC) drugs paving way for self-medication and rampant abuse, major source of dispensing such combination creams by pharmacists, prescriptions by non-dermatologist practitioners and the rapid symptomatic relief. These factors contribute to the increased abuse of TCS and thus the increasing prevalence of steroid modified dermatophytosis and tinea incognito with widespread lesions, multiple areas of involvement and difficult to treat cases [17, 34, 35]. In an Indian cross-sectional study, it was observed that combination of topical antifungal and potent corticosteroid is most commonly prescribed by non-dermatologist practitioners [34].

Usage of topical corticosteroid suppresses the local inflammation and scale formation, interferes with host immunity and eventually contributes to recurrence or relapse once patient stops using topical corticosteroid [36, 37]. Experts opined that the use of all classes of TCS should be strictly avoided in the management of dermatophytosis. According to the panelists, itraconazole 200 mg/day is the preferred oral antifungal drug over terbinafine 250 mg twice daily and should be combined with topical antifungal having significant anti-inflammatory action like sertaconazole[6], eberconazole [23], ciclopiroxolamine [26] or luliconazole which has a reservoir effect and wide spectrum of action against dermatophytes, especially *Trichophyton mentagrophytes* [21, 38] in these patients, while topical corticosteroid should be withdrawn abruptly.

v. Supplemental Therapy

It has been documented that there is increased trans-epidermal water loss from the skin in dermatophytosis leading to dry skin. Pruritus is a well-known presenting symptom of tinea infection [39]. These findings justify the consensus of the panelists with regard to the use of antihistamines and moisturizers with barrier repair in the management of tinea infections. They also recommended the use of starch free, medicated powder/talc in obese patients which will help to keep the area dry.

6.1.3. Management of Tinea Corporis et Cruris in Pregnancy & Lactation

i. Difference in Clinical Presentation, as Compared to Non-pregnant State

As per the consensus of panelists, dermatophytic lesions in pregnant patients are more inflammatory, with extensive spread and multiple sites of involvement.

ii. Optimal Choice of Antifungal Drugs

As per published literature, the choice of antifungal therapy for treatment of dermatophytosis in pregnancy is depicted in table 4 [40].

iii. Dose and Duration

It is cited in literature that topical antifungal therapy should be continued for at least 2 weeks after complete resolution of symptoms, irrespective of naïve or recalcitrant infection [41]. Experts agreed that duration of topical therapy

should be a minimum of 4 weeks in naïve infections and 6 weeks in recalcitrant infections.

Table 4. *Options for antifungal treatment of dermatophyic infections in pregnancy. [Adapted from Kaul et al. [40]*

Antifungal therapy	Recommendation
Topical	Clotrimazole
	Ciclopirox
	Terbinafine
	Naftifine
	Oxiconazole
Systemic	Not recommended

6.2. Vulvovaginal Infections (VVI)

6.2.1. Diagnosis of VVI

i. Current Trend of VVI in India-Rise of Non-albicans Candida (NAC)

Prevalence of recurrent VVI has been on the rise over the last few years. There has also been an increase in number of young patients affected by VVI. One of the most striking change in the current scenario is the increasing occurrence of non-albicans vulvovaginal candidiasis (VVC), which is considered as the major cause of recurrence, relapse and chronic VVC in India [12]. According to an Indian epidemiological study, the prevalence of NAC was found to be as high as 74% [Figure 2] [42-46].

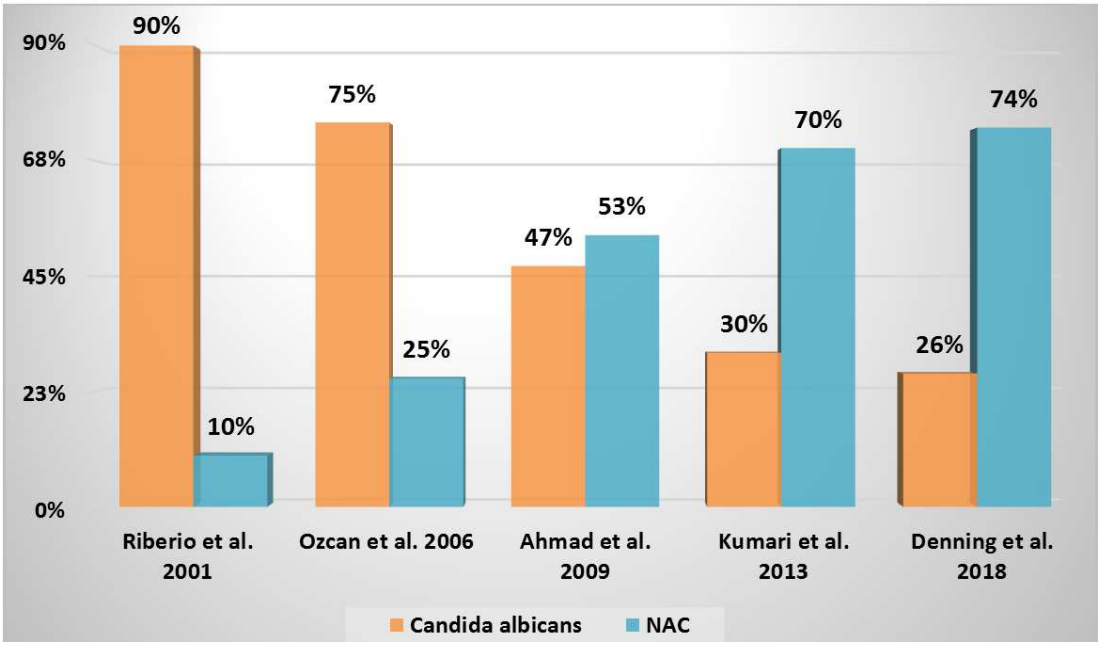

Figure 2. *Rising trends of non-albicans candida (NAC) in VVC in various studies [42-46].*

ii. Diagnosis

The main pathogenic feature in VVI is the presence of inflammation owing to overgrowth of harmful microorganisms. The clinical symptoms arising due this inflammation are neither specific nor sensitive [47, 48]. VVIs are usually diagnosed clinically and treatment initiated accordingly. Since the symptoms are non-specific, it is recommended that diagnosis of VVI should be confirmed by laboratory diagnosis in complicated cases i.e. recurrent forms [12]. This was corroborated in the present consensus, which recommended clinical diagnosis in all cases and laboratory diagnosis in selected cases with complicated VVI, wherein clinical diagnosis is difficult.

Mixed vulvovaginal infections have been increasing over the past few years. According to one Indian study, mixed infections contributed to 25% of all cases of infective vulvovaginitis [49]. Wet mount test can be used as a single utility test to identify causative microorganisms. Expert consensus was in favor of utilization of wet mount test for diagnosis in mixed infections.

One of the key findings in vulvovaginal infections is the change in pH of vaginal mucosa. In case of VVC, the vaginal pH is <4.5, while it is more than 4.5 in case of bacterial vaginosis (BV). A simple pH strip/ litmus paper test can serve as a handy tool to readily differentiate between VVC and BV in mixed infections [50]. This was agreed by the panelists without any modifications to the above statements.

The consensus recommended utilization of Whiff test to confirm the diagnosis of BV, whenever clear cut clinical diagnosis is not possible.

As stated earlier, *non-albicans candida (NAC)* is the commonest cause of VVC in India [12]. Since *NAC* is one of the major cause of rise in recurrence and relapses, panelists opined that fungal culture should be done at least in recurrent and relapse cases to identify the species of *Candida*. This will help to optimize the treatment.

6.2.2. Management of Vulvovaginal Infections

i. Non Pregnant Patients

Drug of choice

Uncomplicated cases of VVI are usually treated with only topical drug therapy, which does give optimal outcomes [51].

It was agreed by the panelists that complicated cases of VVI should be treated with combination therapy of systemic and intravaginal drugs [52]. Regarding the formulation, there is no evidence in literature which cites advantage or preference of one formulation over the other intra-vaginal formulation. There was no consensus among the panelists with regard to the choice of intra-vaginal formulation.

In case of VVC, it is always better to use a drug which will be active against *Candida albicans* as well as NAC. Fenticonazole is one such drug which has many advantages like activity against all causative organisms of VVC, good efficacy, excellent safety profile and unique antifungal mechanism of action by inhibition of secretary aspartate proteinase, which is the major culprit in VVC. Another major highlight of this antifungal is its excellent activity against NAC [24]. Thus, chances of recurrences are less in fenticonazole intra-vaginal therapy, which has been confirmed by clinical studies [24]. Consensus recommendation was using fenticonazole as 1st line drug, and clotrimazole as 2nd line drug for intra-vaginal therapy of uncomplicated as well as complicated VVC.

In complicated VVC, all the existing western world guidelines prefer fluconazole as the 1st line systemic antifungal drug. [51] However, as stated earlier, there is a rise in *NAC* in India which has emerged as the commonest cause of VVC. *NAC* is less sensitive to conventional antifungals [53]. It has been reported that there is rise in fluconazole non-responsiveness in VVC caused by *Candida albicans* as well as *NAC* [54]. As per current consensus, itraconazole emerged as the systemic antifungal drug of choice, owing to its good clinical efficacy. One of the major reasons for such better effect of itraconazole even in *NAC* might be the "post antifungal effect", which is persistence of antifungal action after reduction in dose/stoppage of antifungal drug [55]. Panelists also recommended use of itraconazole as preferred drug in case of clinical non-response to fluconazole. Experts recommended that intravaginal boric acid/ liposomal amphotericin B could be tried in cases of VVC, which are less responsive to conventional antifungal drugs.

As per Center for Disease Control (CDC) 2015 guidelines on management of BV, non-recurrent BV is treated with intravaginal monotherapy and the preferred drug is metronidazole [56], and this was corroborated by the panelists.

Oral therapy in BV is indicated only in selected patients with no/ less response to intravaginal therapy, poor compliance to intravaginal therapy and recurrent form. In such cases, metronidazole is the preferred drug [56] and this was in agreement by the panelists, while 2nd and 3rd preference was clindamycin and tinidazole. One of the major issues with use of oral metronidazole is the increased incidence of candidiasis, in which case, oral clindamycin is preferred [57].

In Indian scenario mixed infections are common, and therefore single drug or combination of drugs that will be active against bacteria as well as fungus is a more suitable choice [49]. This was agreed upon by the experts who concurred that intravaginal drug of choice in such cases should be fenticonazole, followed by fixed dose combination of clotrimazole and clindamycin. Panelists also opined that systemic itraconazole or metronidazole should be added if symptoms do not resolve with intravaginal antifungal therapy, depending on the clinical presentation.

Dose and duration

In uncomplicated VVI, short course intravaginal therapy gives optimal outcomes [51]. The dose and duration of therapy needs to be increased in case of complicated VVI, particularly VVC [51] One of the major reasons for this is rise in *NAC* [46]. Consensus was in agreement with these findings.

Most preferred regimen of fenticonazole in uncomplicated VVC was 1 day therapy, while 2-day therapy was preferred in case of complicated VVC. Most preferred 2-day regimen was day 1 and day 3. This might be explained by vaginal reservoir effect of fenticonazole, which is around 72 hours [52]. Metronidazole 0.75% gel once daily for 5 days was preferred for non-recurrent BV.

After analyzing the evidences in published literature, recommended dosage of itraconazole in uncomplicated and complicated VVC was 200 mg BD for 1 day and 100 mg BD for 3 days respectively [52]. Given the rise of NAC, this dose and duration is expected to be insufficient to get optimal results. Panelists opined that itraconazole should be used in the dose of 200 mg twice daily for 1 day in uncomplicated VVC and 200 mg/day for 7 days in complicated VVC, while oral metronidazole 500 mg twice daily for 7 days is preferred over clindamycin 300 mg BID x 7 days or Tinidazole 1 gm OD x 5 days in recurrent BV.

ii. Pregnant Patients:

Antifungal/ antibiotic drug

It is recommended in all the existing guidelines that systemic antifungal and antibiotic therapy should be strictly avoided in pregnancy, at least in the first trimester. This is due to the increased risk of birth defects in newborn. The recommendation for treating VVI in pregnancy is by intravaginal antifungal or antibiotic, depending on the type of VVI [51, 52]. Categories of antifungal and antibacterial drugs are depicted in table 5 [41, 58-62].

Expert consensus regarding choice of intravaginal drugs was the same as that for non-pregnant patients. As per the Delphi responses, use of systemic antifungal drugs was not recommended by the experts. In case of recurrent BV, less response to intravaginal therapy, or poor patient compliance to intravaginal therapy, consensus was in favor of use of metronidazole as the preferred systemic drug of choice. They opined that these systemic antibiotics should be given from 2nd trimester onwards and strictly avoided during the 1st trimester. This was in corroboration with that of guidelines for management of bacterial vaginosis laid down by CDC [56].

Table 5. *Antifungal and antibacterial drug safety categories in pregnancy & lactation [Adapted from Prabhu et al, USFDA]. [41, 58-62].*

Antifungal	Pregnancy			Lactation	
	USFDA category	Evidence	Recommendations/s	Level	Recommendation/s
TOPICAL					
Clotrimazole	B	1	Topical antifungal of choice	L1	Preferred choice
Other azoles	C	1	Topical antifungal of choice	L1	Preferred choice
Ciclopirox	B	Less evidence, increased risk not documented	Can be used probably	L3	Minimum chances of systemic absorption
Terbinafine	B	Less evidence, increased risk not documented	Can be used	L2	Minimum chances of systemic absorption
SYSTEMIC					
Itraconazole	C	2	Risk	L2	Use with caution
Terbinafine	B	Minimum data	Avoid	L2	Avoid usage for long period
Fluconazole	C/D (in 1st trimester)	2	Risk	L2	Can be used
Griseofulvin	C	2	Avoid	L2	Avoid
Antibacterial					
INTRAVAGINAL:					
Clindamycin	B	1	Avoid in 1st trimester	NA	Use with caution
Metronidazole	B	Minimum data	Use with caution	NA	Use with caution
SYSTEMIC:					
Clindamycin	B	1	Avoid in 1st trimester	NA	Use with caution
Metronidazole	B	Minimum data	Use with caution	NA	Use with caution

Where: USFDA category A indicates clinical data showing no risk to fetus; category B indicates that no clinical data is present/ clinical data suggests no risk but animal studies show adverse effects on fetus/ no clinical data but animal studies show minimum or no risk to fetus; category C indicates clinical data and animal studies are not available/ clinical data not available and animal studies show risk.

Evidence: 1 indicates randomized control trial/ systematic review/meta-analysis; 2 indicates non-randomized/ quasi experimental studies

Level in lactation: L1 indicates safest; L2 indicates safe; L3 indicates safer; L4 indicates possibly dangerous, L5 indicates contraindicated.

NA: Not available.

Dose and duration

Recommendations for dose and duration of intra vaginal antifungal/ antibiotic was similar to that of non-pregnant females.

iii. Supportive Therapy in Management of VVI:

It is a known fact that common finding in any type of VVI is the reduction in number of *Lactobacillus* and increased pH of vaginal mucosa [62]. Also, it has been found in various randomized clinical trials that use of probiotic along with core antifungal/ antibiotic therapy in VVI increases cure rate, induces rapid recovery and helps to reduce the risk of recurrence and relapse [63-65]. Experts opined that vaginal probiotic therapy along with core therapy helps to reduce recurrence/relapse rates. Although there is no conclusive evidence for optimal duration of vaginal probiotic therapy, based on clinical experience, panelists gave consensus in favor of 1 month therapy. There was no consensus on the statement that probiotic along with core therapy increases cure rate in VVI.

As per Middle East and Central Asia (MECA) and Royal College of Obstetrics and Gynecology (RCOG) guidelines, use of daily intimate wash with hypoallergenic lactic acid based solution is recommended [66, 67]. This helps to reduce the recurrence and relapse in VVI, which was confirmed in a RCT [68]. Experts recommended the routine use of hypoallergenic intimate washes, as it will help to reduce recurrence/ relapse after completion of main therapy in VVI.

There is growing evidence that male partner of affected female acts as a constant source of re-infection for such females. Since males are asymptomatic, it does not warrant medical attention on the patient's part [69]. Hence, it was recommended that male partners should also be treated in case of recurrent, relapse or chronic VVI.

6.3. Treatment Algorithm

The experts proposed algorithm for treatment of dermatophytosis (figures 3 & 4) and VVI (figure 5).

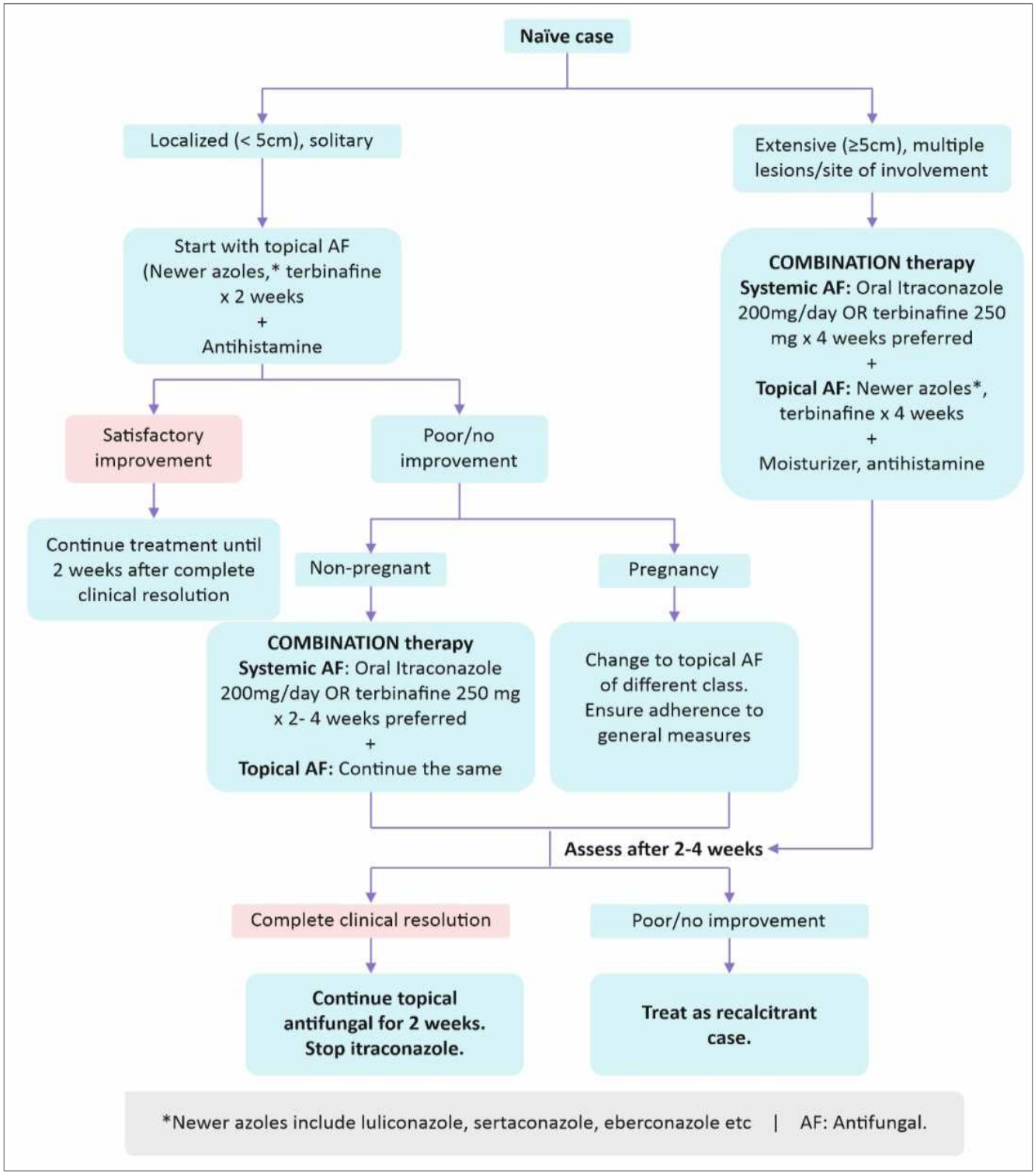

Figure 3. *Algorithm for treatment of naïve cases of dermatophytosis.*

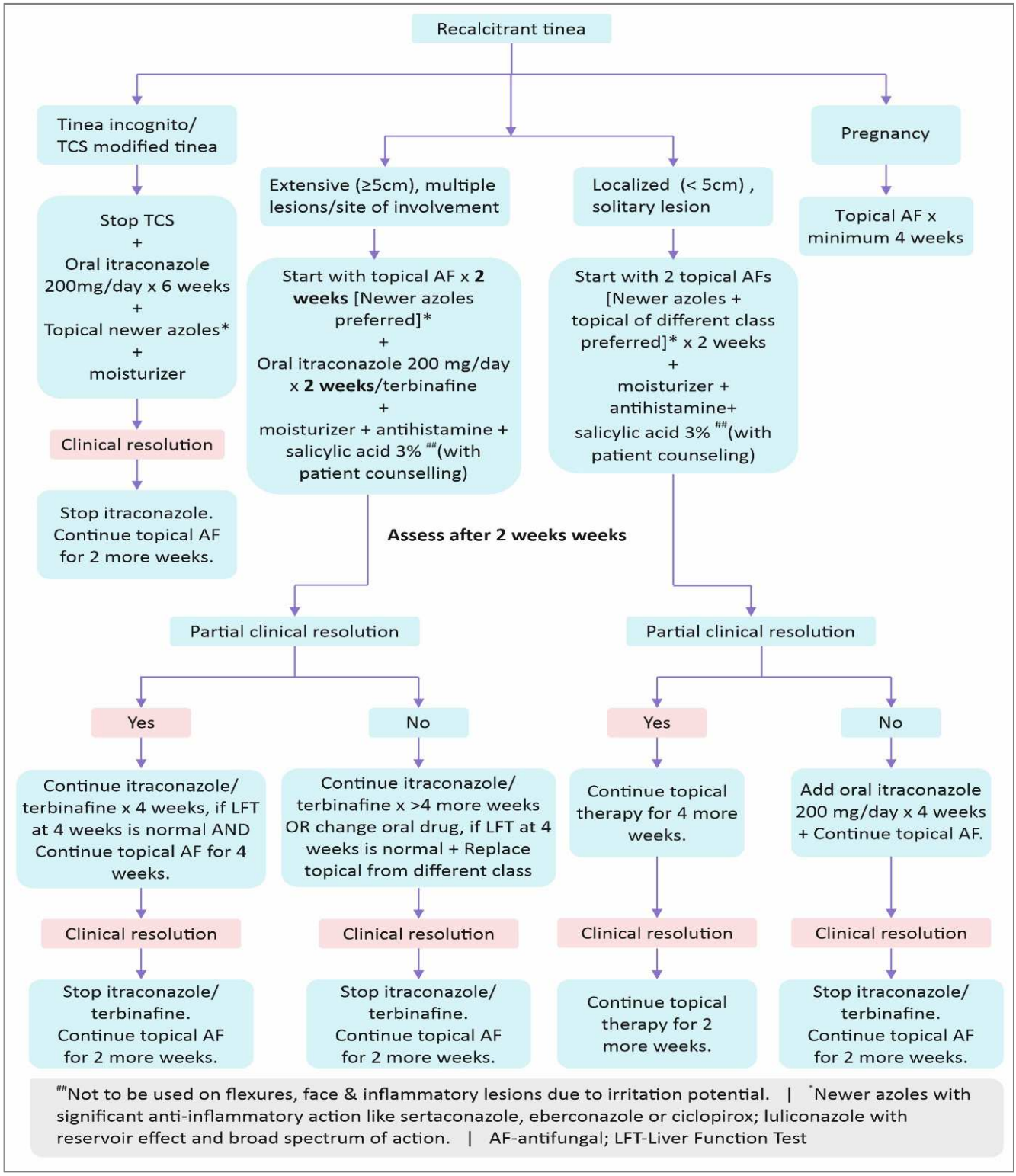

Figure 4. *Algorithm for treatment of recalcitrant dermatophytosis and steroid modified dermatophytosis.*

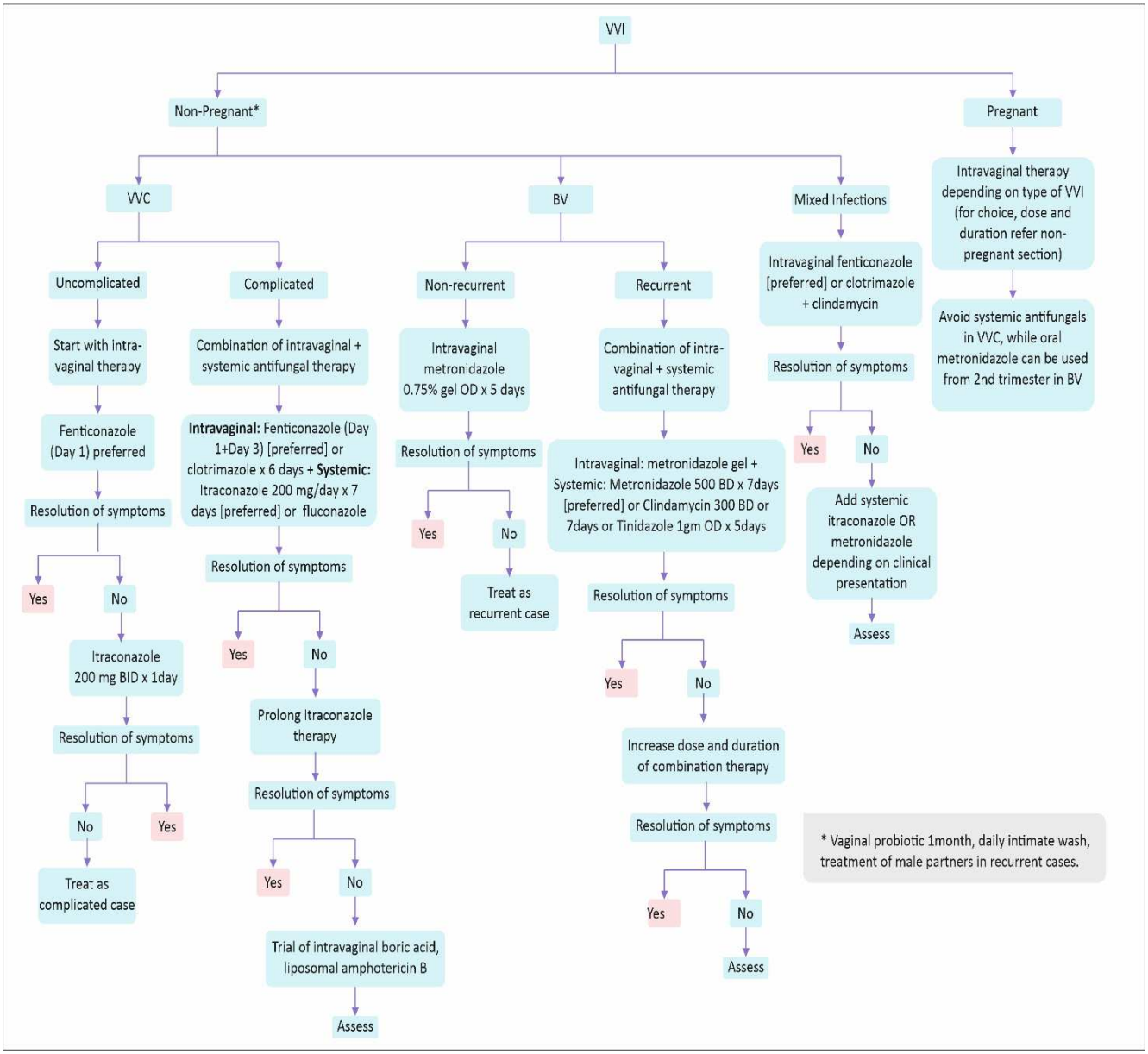

Figure 5. *Algorithm for treatment of vulvo-vaginal infections (VVI).*

7. Conclusion

In the context of increase in the prevalence of vulvovaginal infections and dermatophytosis among females, which have evolved as major health concerns in the recent years, there is a felt need for Indian guidelines on management of these infections with special focus on pregnancy. Hence, the present consensus was an attempt to bridge these need gaps in the management of dermatophytosis and vulvovaginal infections. This consensus along with the algorithms, formulated based on the currently available evidence and experience, will help the clinicians to choose an appropriate drug, dose and duration in various contexts, which in turn will result in an effective management of these patients. Further therapeutic studies in this arena will pave way for revalidation of this consensus in the years to come.

Conflicts of Interest

There are no conflicts of interest declared by the authors. The design, methodology and content of the present research work is not prejudiced by fund supporters.

Research Involving Human Participants and/or Animals & Informed Consent

The present consensus was done in accordance with ethical guidelines of latest amended Helsinki's declaration. The methodology adopted for the present research work does not require ethics committee approval and informed consent for participation.

Statement by Authors

Manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

Source of Funding

The present consensus was supported by Glenmark Pharmaceuticals Ltd.

Author's Contributions

Dr. S Kandhari and Dr. Sunil Dogra designed the methodology for the present consensus. The presentations regarding current scenario of VVI and dermatophytosis, challenges in management and need gaps in literature and clinical practice were done by Dr. R Talukdar, Dr. V. Viswanath. Dr. C Nayak and Dr. R. Madhu framed questionnaire for laboratory diagnosis and treatment of dermatophytosis. Dr. P. Prabhat, Dr. D. Banerjee, Dr. N. Singh, Dr. P. Gopinath, Dr. M. Patil and Dr. J. Shreedhar contributed in the development of questionnaire for laboratory diagnosis and treatment of VVI. All the panelists were actively involved in the formation of consensus, and preparing, reviewing and editing the manuscript. The present version of manuscript was approved by all the panelists.

Disclaimer

Following the recommendations of the present consensus will not ensure optimal outcomes in the management of each and every case of dermatophytosis and VVI. The decision regarding choice of diagnostic method, drug, its dose and duration should be made by the physician depending on the clinical presentation of the disease.

Acknowledgements

The panelists would like to express sincere appreciation to Dr. Harshal Mahajan, Dr. Dhiraj Dhoot, and Dr. Hanmant Barkate from Medical services, Glenmark Pharmaceuticals Ltd. for collating, evaluation of data and modified Delphi responses and manuscript preparation.

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