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Cover picture

CAVENTOU, PELLETIER, AND QUININE
(About 1820)

The team of Parisian pharmacists, Pierre-Joseph Pelletier and Joseph-Bienainié Caventou, isolated many plant constituents in their apothecary shop; their greatest contribution was extraction of quinine from cinchona (Peruvian) barks.

Management of common thyroid disorders in pregnancy

Introduction

Thyroid disorders in pregnancy are easily missed because of non-specific symptoms or changes in metabolism and hormone levels that normally occur in pregnancy. These changes require cautious interpretation of thyroid function tests in pregnancy. The prevalence of overt hyperthyroidism and hypothyroidism is between 0.4% and 1.7% and 2% and 3% respectively.

Physiological changes in pregnancy

Clinical features such as heat intolerance, peripheral vasodilation, tachycardia, palpitations, wide pulse pressure, and systolic flow murmurs are common to both pregnancy and hyperthyroidism. In iodine deficient areas the gland may even appear enlarged and goitrous. Human chorionic gonadotrophin (hCG) produced by the placenta in the first week of conception peaks at 10 weeks before decreasing and reaching a plateau at 20 weeks. Because of close homology of the beta-subunit of hCG to thyroid stimulating hormone (TSH) it may stimulate the thyroid to suppress TSH to the hyperthyroid range. Compared with preconception levels TSH concentrations are low throughout pregnancy, lowest in the first trimester, increasing in the second and third trimesters.

A pregnant woman has to increase her output of thyroxine (T4) during pregnancy for several reasons. It is increasingly metabolised owing to activity of a placental enzyme which converts thyroxine (T4) to reverse triiodothyronine T3 (rT3), and triiodothyronine (T3) to diiodothyroine (T2). Increased maternal glomerular filtration of iodine causes renal loss while the fetal demand for iodine increases.

High oestrogen levels in pregnancy increase hepatic output of thyroxine binding globulin (TBG) and its half-life. This leads to a sharp rise of total thyroxine (TT4) and total triiodothyronine (TT3) between six and twelve weeks of gestation and even more steeply thereafter, to stabilise around mid-gestation, but the free thyroxine levels remain lower than normal.

Hyperthyroidism in pregnancy

Graves' disease is the most common cause of hyperthyroidism in pregnancy, and accounts for over 80% of cases. Exophthalmos, onycholysis, pretibial myxoedema, high levels of T4, T3, or thyroid receptor stimulating antibodies (TRabs) support a diagnosis of Graves' disease.

When caused by autoimmune thyroid disease it is most likely to occur in the first trimester or the post-partum period because of immune suppression that occurs in pregnancy. Gestational thyrotoxicosis refers to hyperthyroidism caused by raised levels of hCG which activate the TSH receptors. Twin pregnancies and molar pregnancies are associated with higher levels of hCG, and a higher incidence of hyperthyroidism.

Women with hyperemesis gravidarum also may have abnormal thyroid function tests with high free thyroxine measurements. Absence of a goitre, ophthalmopathy, and hyperthyroid symptoms antedating pregnancy favour a diagnosis of hyperemesis gravidarum. It is a self-limiting condition that resolves by 16-18 weeks when hCG levels decline and vomiting ceases. It rarely occurs with hCG levels less than 50 000 IU/ ml. As total T4 and T3 levels are increased in normal pregnancy and thyrotoxicosis, a diagnosis can be established only by a low TSH level coupled with elevated T4 and or T3 levels.

Post-partum thyroiditis is an autoimmune disorder occurring within the first year of partus. It usually presents with transient hyperthyroidism in the first six months followed by transient hypothyroidism and return to the euthyroid state by one year. Anti-thyroid drugs are ineffective as it is a destructive process and not due to over-production of thyroxine; propranolol may be used for suppressing adrenergic symptoms. Thyroxine may be required if the TSH remains high or if symptomatic hypothyroidism occurs.

Subacute thyroiditis also may cause transient hyperthyroidism and present as a painful or tender

thyroid gland; a raised ESR and high thyroglobulin levels are suggestive laboratory findings. Aspirin or nonsteroidal anti-inflammatory agents may be used for pain relief, failing which, oral steroids can be used.

Treatment of maternal hyperthyroidism

Preconception counselling is essential to allow the woman to choose the best treatment option to control the disease before pregnancy.

Once diagnosed as hyperthyroidism treatment is mandatory to reduce morbidity to both mother and fetus. Inadequate treatment of the mother can result in complications such as atrial fibrillation, proximal muscle weakness, weight loss, anxiety, preeclampsia and thyroid storm. Left ventricular dysfunction leading to congestive cardiac failure could occur, especially in the presence of anaemia, infection or preeclampsia. The fetus too may suffer from intrauterine growth retardation, low birth weight or premature birth.

The antithyroid drugs (ATDs), carbimazole or methimazole (MMZ) and propylthiouracil (PTU) are used for maternal hyperthyroidism. The goal of therapy is to maintain maternal serum free thyroxine (fT4) at just above the upper limit of normal for pregnancy using the lowest ATD dose possible. This is to minimise the potential for over-treatment which could result in fetal hypothyroidism as both ATDs cross the placenta.

Use of MMZ has been associated with congenital abnormalities unlike PTU. The latter has been responsible for acute liver failure. For these reasons PTU is the preferred treatment in the first trimester as well as before conception. After the first trimester PTU can be replaced by an equivalent dose of MMZ to prevent development of liver damage. (100 mg of PTU=7.5 mg of MMZ).

After partus Graves' disease may worsen, necessitating use of ATDs. PTU is preferable post-partum because its excretion in breast milk is small and because it suppresses peripheral conversion of T4 to T3. But either can be used as they are now considered safe in lactating mothers.

Beta blockers, (eg. propranolol) can be used to control adrenergic symptoms occurring in hyperthyroidism. However, long term use can cause fetal bradycardia, neonatal hypoglycaemia and intrauterine growth retardation. For these reasons labetalol is recommended for use in pregnancy and lactation.

Surgery for hyperthyroidism may have to be considered if large doses of ATDs are required for control or serious side-effects occur. In preparation for surgery short courses of beta blockers or oral iodine can be used. Surgery is best timed for the second trimester as risk of miscarriage is high in the first trimester, and of preterm labour is high after 24 weeks.

Radioiodine is absolutely contraindicated in pregnancy and lactation because of serious effects it has on the thyroid of the fetus and the baby.

Monitoring treatment

Maternal fT4 and TSH should be monitored every 2 to 4 weeks after initiation of ATDs, and every 4 to 6 weeks after achieving target levels, A decrease of TRabs levels following treatment may allow for smaller doses of ATD in the second trimester, and discontinuation in the third trimester. When present in high titre TRabs can cross the placental barrier and cause stimulation of the fetal thyroid to cause fetal hyperthyroidism. Before delivery the fetus is protected by the ATD that crosses the placenta, but following partus neonatal hyperthyroidism may occur within the first 72 hours and last 2 to 3 months, necessitating treatment.

Ultrasonography is the best non-invasive method of monitoring fetal hypothyroidism. The presence of a goitre is highly suggestive of hypothyroidism in the fetus, and ATD treatment should then be stopped, as the risk of maternal hyperthyroidism in pregnancy is much less than the risk of fetal hypothyroidism to fetal and neonatal growth and mental development. There could be tracheal obstruction and obstructed labour consequent to the enlarged thyroid gland.

Maternal hypothyroidism

The fetal thyroid starts producing thyroid hormone at about 10 weeks of gestation, so in the first trimester the fetus is entirely dependant on the mother for its

thyroxine. The gland increases its production until it plateaus around 30 weeks.

In the first 18 weeks of pregnancy maternal thyroxine is essential for normal brain development. Maternal hypothyroidism results in impaired mental function of the baby, even in clinically unsuspected hypothyroidism.

Maternal hypothyroidism must be suspected in women who have had thyroid surgery, radioiodine treatment or shown antibodies, specially anti-thyroid peroxidase. Thinning or falling of hair, muscle cramps, constipation and carpal tunnel syndrome should also alert the clinician to suspect maternal hypothyroidism.

Risk of pregnancy complications is markedly increased in women with untreated overt hypothyroidism. Spontaneous first trimester loss, prematurity, perinatal death, abruption and eclampsia are the common complications. But the risks are markedly reduced by timely diagnosis and treatment.

In diagnosed hypothyroid women the replacement dose should be monitored before planned pregnancy to ensure a TSH value of 0.3 to 2.5 mU/L. Where such estimations are not available, as a practical guide, the patient may be requested to increase the pre-pregnancy dose by 100 microgram per week when the pregnancy is confirmed. Alternatively TSH may be monitored once a month and the dose of thyroxine adjusted accordingly. TSH should be monitored monthly until 20 weeks and then bimonthly to maintain it at less than 2.5 mU/L. After delivery the dose can be reverted to pre-pregnancy levels. The drug should be taken on an empty stomach at least half hour before breakfast. As oral iron can bind to T4 the timing of iron should be at least two hours before or after T4 ingestion.

Thyroid nodule in pregnancy

When detected in pregnancy they have a higher risk of malignancy because of selection or sampling bias, since many women do not have any systematic health examination until they become pregnant. The evaluation is similar to that of the non-pregnant woman. Fine needle aspiration should be offered if the nodule is more than two cm, if detected before 20 weeks, or if there is lymphadenopathy or rapid enlargement. If the cytology confirms papillary thyroid carcinoma or is suspicious of malignancy it could be removed in the second trimester to avoid the risk of miscarriage if done earlier, or preterm labour if done in the third trimester. If the nodule is less than 2 cm and not showing rapid growth or lymphadenopathy it is reasonable to postpone surgery until after pregnancy and use daily thyroxine to suppress the gland.

Practice points

- ATDs cross the placenta and can affect the development of the fetal thyroid and brain with dire consequences. Hence it is better to err on the side of under-treatment; over-treatment may lead also to thyroid enlargement in the baby causing tracheal obstruction, difficult labour, or necessitating a caesarean section.

- ATDs are secreted in breast milk, PTU to a lesser extent than MMZ, but have not been found to cause harm.

- Thyroid receptor antibodies, which are present in Graves' disease, cross the placental barrier and stimulate receptors in the baby causing neonatal hyperthyroidism. Fetal thyrotoxicosis can cause goitre, oligohydramnios, intrauterine growth retardation and accelerated bone maturation.

- Fetal thyrotoxicosis may manifest as irritability, failure to thrive, jaundice, diarrhoea, craniosynostosis, exophthalmos and hepatosplenomegaly. Treatment may be required for about 20 weeks until antibody levels wane.

Suggested reading

1. Stagnaro-Green A. Overt hyperthyroidism and hypothyroidism during pregnancy. *Clinical Obstetrics and Gynaecology* 2011; **54**: 478-87.

2. Abalovich M, Amino N, Barbour LA, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society

Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2007; 92 (suppl 8): S 1-47.

3. Momotani N, Yamashita R, Makino F, et al. Thyroid function in wholly breast feeding infants whose mothers take high doses of propyl-thiouracil. *Clinical Endocrinology* 2000; **53**: 177-81.

4. McKenzie JM, Zakarija M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. *Thyroid* 1992; **2**: 155-9.

5. Hay ID. Nodular thyroid disease diagnosed in pregnancy: how and when to treat. *Thyroid* 1999; **9**: 667-670.

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Long-acting beta$_2$ agonists for childhood asthma

Summary

Long-acting beta$_2$ agonists are currently overprescribed in children. They are also often used inappropriately as first-line therapy and are not recommended for children aged five years or less.

Due to the paucity of paediatric clinical trials, the evidence for the efficacy and safety of long-acting beta$_2$ agonists in children is limited. There is little evidence that they reduce the risk of severe exacerbations and some evidence that they may actually increase the risk.

The regular use of long-acting beta$_2$ agonists may also result in a loss of protection against exercise-induced bronchoconstriction, and the development of tolerance to short-acting beta$_2$ agonists.

Long-acting beta$_2$ agonists are only one option for children whose asthma is not adequately controlled with inhaled corticosteroids alone – the other options being an increase of inhaled corticosteroid dose or the addition of a leukotriene receptor antagonist. For children whose major ongoing symptoms are activity related, the addition of a leukotriene receptor antagonist is the preferred option.

Key words: inhaled corticosteroids, leukotriene receptor antagonists

(Aust Prescr 2012;35:111-3)

Introduction

Australian guidelines for persistent childhood asthma advocate a stepwise approach to therapy with preventer drugs.[1] These guidelines highlight that the vast majority of children requiring preventer therapy will be well controlled on either low-dose inhaled corticosteroids or a leukotriene receptor antagonist. Long-acting beta$_2$ agonists should be given only to children who remain symptomatic on optimal doses of inhaled corticosteroids.

There is limited evidence for the efficacy of long-acting beta$_2$ agonists in children,[2] but combination therapy (inhaled corticosteroids and long-acting beta$_2$ agonists) is commonly prescribed as first-line when preventer therapy is needed. Combination therapy now represents over 40% of prescribed preventer therapy in children. Based on the frequency of asthma patterns in children and the stepwise approach advocated by the current National Asthma Council of Australia guidelines,[1] combination therapy should represent no more than 10% of prescribed preventer therapy in children and probably less, given the availability of alternative step-up options.

A greater concern is that combination therapy now represents 20% of **all** prescribed asthma medication (preventers and relievers) in pre-school children.[3] This is outside the prescribing indications for combination therapy and no evidence exists for the efficacy or safety of long-acting beta$_2$ agonists in this age group. Combination therapy is also often inappropriately prescribed for intermittent, rather than regular, use.

Efficacy of long-acting beta$_2$ agonists in children

A Cochrane review has assessed the addition of long-acting beta$_2$ agonists to inhaled corticosteroids for persistent asthma in children.[2] It included 25 randomised trials, representing 31 control-intervention comparisons, in 5572 children. Importantly, no studies included children less than four years of age.

There were 24 comparisons of adding long-acting beta$_2$ agonists or placebo to a constant dose of inhaled corticosteroids. These trials showed a predictable small and probably not patient-important improvement in lung function. There was no significant reduction in exacerbations in the children taking regular long-acting beta$_2$ agonists.

Seven studies compared the addition of long-acting beta$_2$ agonists with an increased dose of inhaled corticosteroids. The children on long-acting beta$_2$ agonists had significantly improved lung function and short-term linear growth when compared to those on higher dose inhaled corticosteroids. However, there was a non-significant increase in exacerbations requiring oral corticosteroids and hospitalisation (which the authors concluded required further examination).

Another Cochrane review highlighted the difference in the effectiveness of long-acting beta$_2$ agonists in children versus adults.[4] This review compared the addition of long-acting beta$_2$ agonists to inhaled corticosteroids versus higher dose inhaled corticosteroids, in both adults and children with suboptimal asthma control despite low-dose inhaled corticosteroids. In adolescents and adults the combination of long-acting beta$_2$ agonists and inhaled corticosteroids was modestly more effective in reducing the risk of exacerbation requiring oral corticosteroids than a higher dose of inhaled corticosteroids. However, in children, combination therapy did not lead to a significant reduction, but rather a trend toward an increased risk of severe exacerbations and hospital admission.[4]

A further Cochrane review examined the addition of long-acting beta$_2$ agonists to inhaled corticosteroids versus inhaled corticosteroids alone as first-line therapy for persistent asthma in adults and children who had previously taken steroids. This review concluded that the 'current evidence does not support the use of combination therapy as first-line preventive treatment, without a prior trial of inhaled corticosteroids'.[5] While the combination of budesonide and eformoterol is approved for patients aged 12 years and over, there are limited paediatric data.

Safety of long-acting beta$_2$ agonists in children

The Cochrane reviews raised safety concerns about an increased risk of severe exacerbations and hospitalisation with long-acting beta$_2$ agonists.[2,4] These observations are consistent with a recent meta-analysis which found an increased risk of severe and life-threatening asthma exacerbations associated with long-acting beta$_2$ agonists, even when they were used with concomitant inhaled corticosteroids.[6] This finding contradicts previous suggestions that the increased risk of severe exacerbations with long-acting beta$_2$ agonists is only seen in patients treated with long-acting beta$_2$ agonists alone.

A possible explanation for the increased risk of severe exacerbations is the development of tolerance to

short-acting beta$_2$ agonists, resulting in a diminished response to the child's normal rescue therapy. This assumption is supported by a recent study in children with poorly controlled exercise-induced asthma, despite inhaled corticosteroids. The trial compared montelukast versus long-acting beta$_2$ agonists as add-on therapy to inhaled corticosteroids. Long-acting beta$_2$ agonist therapy was associated with the development of tolerance to both protection against exercise-induced bronchoconstriction and the response to short-acting beta$_2$ agonists.[7]

These safety concerns have led the US Food and Drug Administration (FDA) to recommend that long-acting beta$_2$ agonists should only be used as combination therapy to ensure that children continue to receive an inhaled corticosteroid. To limit exposure, the long-acting beta$_2$ agonist should be withdrawn once good asthma control has been achieved.[8] More recently the FDA issued a requirement for further trials in children, adolescents and adults, to 'provide data in a timely fashion that will clarify the safety risks associated with long-acting beta$_2$ agonists when used concurrently with inhaled corticosteroids, and to inform the safe use of these medications for the treatment of asthma'.[9]

Comparison with other treatments

The currently recommended options for children whose asthma is not adequately controlled on inhaled corticosteroids alone are:

- adding a long-acting beta$_2$ agonist
- adding a leukotriene receptor antagonist
- increasing the dose of inhaled corticosteroids.

Before intensifying the treatment of poorly controlled asthma it is important to first exclude other factors contributing to poor control. These include incorrect diagnosis, poor adherence, inappropriate delivery device and poor inhaler technique.

When comparing the addition of long-acting beta$_2$ agonists to an increased dose of inhaled corticosteroids, current evidence suggests that while regular use of long-acting beta$_2$ agonists will predictably improve lung function, the risk of exacerbation appears, if anything, to increase.[2,4]

A randomised triple crossover study in 182 children aged 6-17 years of age who had uncontrolled asthma on 100 microgram of fluticasone propionate twice daily also provides relevant comparative information.[10] These children received 16 weeks on each of the following therapies, in random order:

- 250 microgram of fluticasone twice daily (inhaled corticosteroid step-up)
- 100 microgram of fluticasone plus 50 microgram salmeterol twice daily (long-acting beta$_2$ agonist step-up)
- 100 microgram of fluticasone twice daily plus 5 or 10 mg montelukast daily (leukotriene receptor antagonist step-up).

The response was assessed by a composite index comprising exacerbations requiring oral corticosteroids, asthma-control days and forced expiratory volume in one second. Overall the probability of the long-acting beta$_2$ agonist step-up providing the best response was higher (45%), but the probability of having a best response to leukotriene receptor antagonist (28%) or inhaled corticosteroid (27%) step-up was also significant. This highlights the variability of children's responses to these drugs, plus the need to regularly monitor and appropriately adjust each child's therapy.[9]

What is clear is that leukotriene receptor antagonists are superior to long-acting beta$_2$ agonists in protecting against exercise-induced bronchoconstriction as add-on therapy in children already receiving inhaled corticosteroids.[7] Further, in contrast to regular use of long-acting beta$_2$ agonists, leukotriene receptor antagonists are not associated with the development of tolerance to either protection against exercise-induced bronchoconstriction, nor responsiveness to short-acting beta$_2$ agonists.[7] Montelukast has now been listed in the Australian Pharmaceutical Benefits Scheme for add-on treatment (as an alternative to long-acting beta$_2$ agonists) for children aged 6-14 years, who despite inhaled corticosteroids, have ongoing activity (exercise)-related asthma.

Box

Recommendations on rip-up options[11]

In situations where effective control of asthma cannot be achieved with doses of 400 microgram/day budesonide, or 200 microgram/day fluticasone or hydrofluoroalkane-beclomethasone dipropionate or 160 microgram/day ciclesonide, the main step-up options include increasing the inhaled corticosteroids dose or adding a long-acting $beta_2$ agonist or a leukotriene receptor antagonist. In the absence of evidence of safety and efficacy, the use of long-acting $beta_2$ agonists is not recommended in children aged five years or younger. (Strong recommendation, moderate quality evidence).

In children with ongoing exercise-induced symptoms, despite inhaled corticosteroids, adding leukotriene receptor antagonists has been shown to be effective and superior to long-acting $beta_2$ agonists, and does not have the problem of the development of tolerance. (Strong recommendation, moderate quality evidence)

Recommendations

There are few efficacy trials of long-acting $beta_2$ agonists in children with asthma, and no trials have been conducted in children under four years of age. There are ongoing safety concerns with long-acting $beta_2$ agonist use, particularly in children, which require further clarification. Based on current evidence the Thoracic Society of Australia and New Zealand has made recommendations on 'The role of corticosteroids in the management of childhood asthma'[11] (see Box).

In brief, there are three step-up options for children not adequately controlled on inhaled corticosteroids:

- adding a long-acting $beta_2$ agonist
- adding a leukotriene receptor antagonist
- increasing the dose of inhaled corticosteroids.

The addition of a leukotriene receptor antagonist is the preferred option for children with ongoing activity-related asthma. Long-acting $beta_2$ agonists are not recommended for children five years or younger.

References

1. Asthma Management Handbook 2006. Melbourne: National Asthma Council Australia; 2006.
2. Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 2009; CD007949.
3. Phillips CB, Toyne H, Ciszek K, Attewell RG, Kljakovic M. Trends in medication use for asthma in school-entry children in the Australian Capital Territory, 2000-2005. Med J Aust 2007;187:10-3.
4. Ducharme FH, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 2010;CD005533.
5. Ni Chroinin M, Greenstone I, Lasserson TJ, Ducharme FM. Addition of inhaled long-acting beta-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. Cochrane Database Syst Rev 2009;CD005307.
6. Salpeter SR, Wall AJ, Buckley NS. Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events. Am. J Med 2010;123:322-8.
7. Fogel RB, Rosario N, Aristizabal G, Loeys T, Gaile S, Noonan G, et al. Effect of montelukast or salmeterol added to inhaled fluticasone on exercise-induced bronchoconstriction in children. Ann Allergy Asthma Immunol 2010;104:511-7.
8. Chowdhury BA, Dal Pan GD. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. N Engl J Med 2010; 362:1169-71.

9. Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. N Engl J Med 2011;364:2473-5.
10. Lemanske RF, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al. Step-up therapy for children with uncontrolled asthma while receiving inhaled corticosteroids. N Engl J Med 2010;362:975-85.
11. Van Asperen PP, Mellis CM, Sly PD, Robertson CF. The role of corticosteroids in the management of childhood asthma. Sydney: Thoracic Society of Australia and New Zealand; 2010.

Further reading

Van Asperen PP, Mellis CM, Sly PD, Robertson CF Evidence-based asthma management in children – what's new? [editorial]. Med J Aust 2011;194:383-4.

Van Asperen P. What's new in the management of asthma in children? Med Today 2011;12:53-64.

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Professor Peter van Asperen is currently a member of the MSD (Aust) Paediatric Respiratory Physician Advisory Board and has received speaker fees from MSD for presentations on management of asthma and wheeze in children. He is a member of the GlaxoSmithKline Paediatric Respiratory Taskforce which has been convened to ensure appropriate prescribing of Seretide in children. His department has received research funding in the past from GlaxoSmithKline, Astra Zeneca, MSD, Boehringer Ingelheim and Altana for involvement in clinical trials but is not currently receiving funding from these companies.

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Vaginal discharge

Abstract

Vaginal discharge is a common symptom in women presenting at general practice, genito-urinary and gynaecology clinics. In women of reproductive age bacterial vaginosis and yeast infections are the commonest problems. In view of other multiple infective and non-infective causes and poor correlation between clinical symptoms and their causes, a systematic approach is essential in management. This article discusses clinical presentation, diagnostic approach and treatment of vaginal discharge in children, adolescents, reproductive age women and post-menopausal women.

Introduction

Vaginal discharge is a non-specific symptom (see table). Use the opportunity to offer cervical screening with pap smear if indicated.

Table. Causes of vaginal discharge

Physiological	
	Cervical ectopy, pregnancy, atrophic vaginitis
Infective	
	STI- *Chlamydia trachomatis, Trichomonas vaginalis, Neisseria gonorrhoeae, Herpes simplex (HSV)* Non-STI- *Gardnerella vaginalis, Candida albicans,* toxic shock syndrome
Neoplastic	
	Vaginal, cervical, endometrial and fallopian tube carcinoma Benign mucosal, cervical, endometrial and fibroid polyps
Iatrogenic	
	Foreign body, drug-induced
Anatomical	
	Fistula

STI = sexually transmitted infections HSV = Herpes simplex virus

History

Taking a detailed history is an important first step. Aim to ascertain whether there is a change in the discharge such as an unusual colour, increased volume, an abnormal smell, irritation, itching or burning. If not, a physiological discharge is the likely cause. It is also important to check why the patient is presenting now and what her current concerns are. Psychosocial factors play a major role in women complaining of vaginal discharge where no infectious aetiology is found.

Enquiry into the sexual history (new partner, cervical smear history, possibility of pregnancy), and previous gynaecological history (recent surgery, miscarriage etc) are important.

Associated symptoms including abnormal bleeding pattern, intermenstrual bleeding or post- coital bleeding, abdominal pain, fever or deep dyspareunia, dysuria, vulval pain, soreness or itching should be documented and appropriate gynaecological investigations and management commenced.

Examination

Examination should include perineal inspection, speculum and bimanual examination as appropriate. Discharge associated unilateral swelling and pain may be due to Bartholin or lesser vestibular (Skene) gland infection.

Investigations

A dry cotton swab applicator can be used to obtain a sample from the vagina and introitus. A "wet slide" can then be mounted on a drop of saline, another on 10% KOH, and examined under low power. On the saline slide normal epithelial cells suggest physiological causes; "clue cells" suggest bacterial vaginosis and motile flagellates are diagnostic of trichomoniasis. Yeast forms and pseudohyphae in a KOH slide is evidence of candidiasis, and a characteristic "fishy" odour on "whiff test" suggests bacterial vaginosis (BV).

Discharge should also be tested on narrow range pH paper. Normal vaginal pH is close to 4.5, but is higher in trichomonasis and BV. More specific tests are needed to diagnose STI. Advantages in referring to a genitourinary clinic include contact tracing and treatment.

Diagnosis and management

Physiological

Clear or whitish-gray, odourless, mucoid discharge which varies with menstrual cycle. No external signs of inflammation, burning, pruritus or erythema. Wet preparation shows epithelial cells, none or few white cells, no pathogenic organisms. Speculum examination may reveal a cervical ectopy.

Management includes reassurance, hygiene, and diathermy or cold coagulation of an ectopy.

Vulvovaginal candidiasis

Thick, white, odourless, curd-like discharge. Intense pruritus, burning, often with dysuria and vulvitis. Examination reveals vulvar and vaginal erythema with adherent thick discharge. KOH preparation shows budding yeast and pseudohyphae.

Treat with azole antifungals. Examples: clotrimazole, 100 mg vaginal suppository 3 days, other azole preparations such as miconazole as intravaginal creams, apply daily for 10-14 days.

Fluconazole (orally) 150 mg, as single dose, nystatin, 100 000 units vaginal suppository, once daily for 14 days are also effective.

Bacterial vaginosis

Thin, white homogeneous discharge, often malodorous ("fishy") increases after intercourse, mild or no pruritus. Normal external examination. Speculum may show presence of characteristic, adherent homogeneous grey discharge.

Diagnosis is by the presence of at least three of the following criteria.

- A thin, homogeneous, grey-white, non-inflammatory discharge adherent to the vaginal walls.
- The presence of clue cells in >20% of the epithelial cells seen on microscopic examination.
- A vaginal pH of 4.5 or higher.
- A fishy odour before or after adding potassium hydroxide (positive "whiff test").

Treatment is recommended for women who are symptomatic. In asymptomatic women, treatment is not required unless surgical intervention is planned (including termination of pregnancy), or pregnancy with a previous history of preterm birth. Treat with metronidazole 500 mg bd for 7 days, or 2 g single dose, metronidazole (topically) 0.75% intravaginal gel 5 g once daily for 5 days, or clindamycin (topically) 2% intravaginal cream 5 g once daily for 7 days.

Trichomoniasis

Copious, frothy, yellow-green vaginal discharge is characteristic, and 10% of patients complain of a foul "fishy" odour. The odour typically increases with sexual intercourse because of the high pH of seminal fluid. Vulval and vaginal pruritus, often with dysuria, are common complaints in patients with trichomoniasis.

Examination may reveal vulval and vaginal erythema, often with excoriation. Speculum examination may show characteristic 'strawberry cervix'. On wet preparation motile, flagellated organisms are seen with increased white cells.

Treat with oral metronidazole 2 g single dose, or 400 mg twice daily for 7 days.

Cervicitis

Cervicitis with *Chlamydia* or *Neisseria gonorrhoeae* may present as vaginal discharge. Cefixime and azithromycin are useful as single dose agents for patients in whom compliance is usually poor. Consider specialist clinic referral.

Syndromic management of vaginal discharge

Patients with typical symptoms, who have low risk of STI, are non-pregnant, and have no abdominal pain or abnormal bleeding can be treated empirically. Empirical treatment should cover BV (which also covers TV) and candidiasis. A single dose oral regimen (eg. metronidazole 2 g and ketoconazole 150 mg) increases compliance but may not be the most cost-effective.

Adding azithromycin (1g single dose; alternatively doxycycline 100 mg twice daily for 14 days) and cefixime or ciprofloxacin will cover *Chlamydia* and *Neisseria* **but if the patient has a high risk for STI** she (and partner) are better managed in an STI clinic. However, patient reluctance to attend such clinics may affect compliance.

Vaginal discharge in menopausal women

Post-menopausal vaginal mucosa, devoid of oestrogen dependant defence mechanisms, is more prone to

vulvovaginitis. In this age group gynaecological cancers, especially cervical carcinoma, may present with a complaint of vaginal discharge. A discharge which is blood stained needs prompt inspection of the cervix and assessment of the endometrium. Carcinoma of the fallopian tubes (an extremely rare cancer) classically presents with profuse clear vaginal discharge.

Vaginal discharge in adolescent girls

Skills and experience working with adolescents are essential in management. Adolescents have different complaints from the parents' understanding of the problem. It is all too common for the adolescent-parent- practitioner to engage in a "don't ask-don't tell" circle when they present with gynaecological issues.

Start the appointment with the parent and the teenager but explain that you always see all the patients alone with nurse-chaperone for part of the consultation. Emphasising that this is routine practice with all adolescents is useful.

Polyp or foreign body may cause copious and purulent vaginal discharge and may be missed unless appropriate examination is undertaken. A bright light and a nasal speculum are helpful if the patient is relaxed, but some may need to be examined under anaesthesia.

Vaginal discharge in children

Vaginal discharge is a relatively common complaint. Vulvovaginitis is the commonest cause.

Anatomically, absence of labial fat pads and close proximity of the vagina to the anus predispose to faecal bacterial contamination. Thin, atrophic, hyperaemic vaginal mucosa because of deficient oestrogenic protection, is particularly vulnerable. Lack of protective *Lactobacillus* colonisation and an acidic environment also contribute to impaired defence.

Poor hygienic practices, synthetic undergarments, hot weather, obesity, irritant soaps and body-wash detergents and masturbation may contribute to the problem.

Streptococcus and *Haemophilus influenzae* are the commonest causative organisms. Worm infestations (eg *Enterobius vermicularis*) needs to be considered as irritation and itching caused by the eggs is a common cause for vulvo-vaginal symptoms in this age group.

Vaginal foreign body is a common cause in children. Children engage in explorative play and explore their bodies. Persistent discharge not responding to treatment should prompt investigations. Vaginoscopy under anaesthesia can be performed with rigid or flexible hysteroscope. Child abuse should not be overlooked as a cause in children presenting with vaginal discaharge.

Summary

Vaginal discharge is a common gynaecological symptom. Common infective causes may be sexually transmitted (*Chlamydia*, *Trichomonas*, *Neisseria gonorrhoeae* or non-STI (bacterial vaginosis, vulvovaginal candidiasis). Non- infective causes need to be considered especially in extremes of age.

Suggested reading

1. Spence D, Melville C. Vaginal discharge. *British Medical Journal* 2007; **335**: 1147-52.

2. Freeto P, Jay S. What's really going on down there? A practical approach to the adolescent who has gynaecological complaints. *Pediatric Clinics of North America* 2006; **53**: 529-45.

3. Weir E. Bacterial vaginosis: more questions than answers. *Canadian Medical Asociation Journal* 2004; **171**: 448-58.

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Self-assessment questions

*Select the **best** response in each question*

1. Characteristic features of the hyperosmolar hyperglycaemic state (HHS) in diabetes include
    a) patients' age below 50 years
    b) plasma bicarbonate less than 15 mmol/l
    c) plasma glucose >30 mmol/l
    d) anion gap <15 mmol/l
    e) plasma Na^+ 140 – 145 mmol/l

2. In the initial management of HHS
    a) the standard intravenous fluid replacement is physiological (0.9%) saline
    b) intravenous bicarbonate is essential in most patients to correct acidaemia
    c) routine intravenous K^+ replacement is advisable
    d) insulin replacement rate is ideally 7 – 10 units/hour
    e) plasma glucose reduction rate is ideally between 5 – 10 millimol/l

3. In moderate/severe diabetic ketoacidosis
    a) the arterial pH is usually between 7.25 – 7.30
    b) the total body fluid deficit is about 3 – 5 litres in an adult
    c) the "anion gap" is likely to be about 20 mmol/l
    d) prophylactic anticoagulation is advisable
    e) total body phosphate content is reduced

Answers to self-assessment questions

Question 1. The best response is **c**; the plasma glucose is nearly always over 30 mmol/l in HHS. The vast majority of patients are over 55 years of age, their plasma sodium is usually over 150 mosm/kg because of dehydration, and the plasma "anion gap" is slightly increased above normal (which is 17 mmol/l). The plasma bicarbonate is usually over 15 mmol/l as they are often not acidaemic or only mildly so.

Question 2. The best response is **a**. Initially, intravenous bicarbonate and routine intravenous K^+ are not recommended. However, as insulin and rehydration take effect the plasma K^+ may fall precipitously, because the former drives K^+ into cells and restoration of GFR by the latter results in a brisk kaliuresis. Plasma K^+ should be frequently assessed to correct hypokalaemia occurring during treatment. Insulin should be given at 0.05 units/kg/hour (3-5 units/hour), and the decrease in plasma glucose should be about 2.5 mmol/hour in adults. Too rapid a fall of plasma glucose may predispose to cerebral oedema.

Question 3. The best response is **e**. A deficiency of total body phosphate is found in all patients with DKA, but there is no evidence to support beneficial effects from phosphate replacement. The arterial blood pH in moderate/severe DKA is in the range 7.00 – 7.20, and the "anion gap" is usually widened to over 25 mmol/l. The total body fluid deficit in an adult with DKA is about 6-8 litres. There is no evidence to support the prophylactic use of anticoagulants in DKA or HHS.

Reference

1. Ramrakha PS, Moore KP. Oxford handbook of acute medicine. 2nd Edition, 2004. OUP, Page 555-63.

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Current information about drug registration

New chemical entities registered

Generic name	Brand name	Dosage form	Manufacturer	Importer	Therapeutic class / use(s)
Bosentan	Safbo	Tablet, 62.5 mg 125 mg	MSN Labs, India	Associated Pharma	Vasodilator antihypertensive
Bosentan	Bosentas	Tablet, 62.5 mg	Cipla, India	Citihealth Imports	Vasodilator antihypertensive
Pramipexol	Sifrol	Tablet, 1 mg 250 mcg 125 mcg	Boehringer Ingelheim, Germany	Hemas Pharmaceuticals	Parkinson's disease

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