What is New About Influenza?
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Introduction
Influenza viruses are segmented, negative-sense, enveloped RNA viruses that belong to the family Orthomyxoviridae. Influenza is a highly contagious acute respiratory disease of global importance that has caused epidemics and pandemics for centuries. The three types of influenza, A, B and C can be distinguished by serological responses to their internal proteins. From a medical point of view, influenza A and B are more important than influenza C, so the following abstract will mainly be focused on influenza A and B.

Origins of Epidemics and Pandemics
The epidemiological success of influenza viruses is largely due to the natural variability of the two surface proteins, haemagglutinin and neuraminidase. Influenza A accounts for most of the serious influenza diseases in humans, mainly because of its high antigenic variability, which allows the virus to escape neutralizing antibody protection. Antigenic variability seen in influenza B is of a much lesser degree and thus accounting for a lesser disease impact when compared to influenza A.

There are two types of antigenic variation. The first type "antigenic drift" occurs in both influenza A and B viruses and is caused by the accumulation of point mutations in the haemagglutinin and neuraminidase genes as a result of the proofreading fault of RNA-dependent RNA polymerase. Antigenic drift is part of the continuing evolution of influenza viruses that accounts for the emergence of new strains (e.g. influenza A H1N1 New Caledonia, influenza A H3N2 Moscow and influenza B Sichuan are predicted to be the prevalent strains in the coming season). The large-scale epidemic that occurs once in a few years on the top of seasonal variation is due to the emergence of a new strain with a substantial difference in antigenicity from the previous one. The most recent example of such large-scale epidemic in Hong Kong was the attack of influenza A H3N2 Sydney in the first few months of 1998.

The second type of antigenic variation "antigenic shift" causes an even more severe impact on humans. Since the genetic materials of influenza viruses are carried in segmented genomes, exchange of the whole segment of genome can occur when two different subtypes are co-infecting the same host cell. This genetic reassortment results in a major change in the phenotype of the virus and often goes un-recognized by pre-existing anti-influenza immunity. The natural hosts for influenza A viruses include aquatic birds, horses, pigs and humans, whereas influenza B is restricted to humans. The current circulating subtypes of influenza A in humans are H1N1 and H3N2, whereas in aquatic birds all haemagglutinin (H1-H15) and neuraminidase (N1-N9) subtypes can be found. Thus aquatic birds serve as a donor gene pool for new subtypes of influenza A, whereas such a gene pool does not exist for influenza B. This explains why antigenic shift only occurs in influenza A viruses.

Over the last century, three global pandemics (H1N1 in 1918, H2N2 in 1957 and H3N2 in 1968) due to antigenic shift of influenza A virus has occurred. The most recent pandemic threat occurred in Hong Kong SAR. In the middle of 1997, an avian subtype (H5N1) of influenza A was found to be associated with serious disease in humans. The H5 subtype influenza virus was previously confined to avian species and was for the first time found to infect humans. The H5N1 infection in humans was later confirmed to be a result of direct zoonotic transmission from chickens. This Hong Kong H5N1 episode has demonstrated that an intermediate host (e.g. pigs) for reassortment of influenza virus gene segments is not always necessary. Birds being a large, mobile, global reservoir of influenza genes serves as the major threat of the next pandemic.
Seasonality
In most parts of the world, influenza epidemic occurs annually and has a consistent seasonal pattern. The winter peak occurs from November to April in the northern hemisphere, and from May to September in the southern hemisphere. Temperate regions normally experience influenza epidemics in late autumn through spring, where the peak activity in one area lasts about 4-6 weeks and spreading to other areas in the region over a period of 2-3 months. In most tropical or subtropical regions, influenza activity occurs throughout the year, with peaks of activity once or twice a year. In Hong Kong, influenza A displays a consistent seasonality with a major peak occurring in February-March and a minor peak in July-August. No distinct seasonality is observed for influenza B. Figure 1 shows the total number of influenza isolates obtained from Hong Kong including outpatients and hospitalized patients. Data collected from the Prince of Wales Hospital on influenza-related paediatric admission reveals a similar seasonal distribution.

Antiviral Agents
Several antiviral agents are available for the treatment and prophylaxis of influenza infection. The first class includes two chemically related compounds, amantadine and rimantadine. These two "conventional" anti-influenza agents block the ion channel of the virus membrane protein M2, thus abolishing its ion exchange function. This M2 channel is important for virus uncoating and for the maintenance of structural and functional integrity of haemagglutinin during its transport to the plasma membrane of virus-infected cells. These two compounds are effective therapeutically when given within 48 hours of the onset of symptoms, and also prophylactically when given during the period of exposure in a normal epidemic or outbreak situation. A major problem of these two conventional compounds is the high incidence of neurological side effects, though rimantadine has a better safety profile. Another concern about their uses in particular for prophylaxis is the rapid emergence of resistance. In addition, amantadine and rimantadine have no activity on influenza B virus. Another "conventional" compound that has antiviral activity against influenza A and B viruses is ribavirin, a synthetic purine nucleoside analog. For the treatment of respiratory tract infections, ribavirin needs to be administered in an aerosol form, whereas oral administration is of uncertain values. Ribavirin inhibits both transcription and replication by causing nucleotide incorporation errors, and resistant mutants are rare. At present, ribavirin is mainly used for severe cases of respiratory syncytial virus infections.

The second class of anti-influenza agents targets the neuraminidase surface protein. This "newer" class includes zanamivir and oseltamivir. Both are neuraminidase inhibitors that are effective for influenza A and B viruses. Neuraminidase inhibitors act by hindering virus penetration through respiratory tract secretions, by inhibiting the release of progeny virions from the infected cell surface, and by promoting self-aggregation of progeny virions. The marketed formulation of zanamivir is a dry powder for administration by oral inhalation. This targeted delivery to the surface of respiratory tract achieves a high local concentration of the drug with minimal systemic absorption, thereby reducing the potential for side effects and drug interactions. In treatment studies, the reported adverse effects appear to be related to the underlying influenza. No acute bronchospasm or respiratory tract irritation was found with inhaled zanamivir during clinical trials, but these complications have been reported post-marketing. In general, inhaled zanamivir appears to be tolerated in mild-to-moderate asthma but its tolerability remains to be established in those with serious bronchopulmonary disease and those requiring ventilatory support. Oseltamivir is available in capsule form (the suspension form being licensed in some countries is not yet available in Hong Kong). The bioavailability of the active compound is about 80% after oral administration of the prodrug. Systemic exposure to oseltamivir is about 25% higher in the elderly, but tolerance is good and dose adjustment is generally not necessary. However, dosage adjustment is indicated for

Figure 1. Influenza isolation in Hong Kong SAR 1997-2000.
advanced renal insufficiency. Oseltamivir has been generally well tolerated. The most frequent adverse effect is nausea of mild-to-moderate intensity, vomiting is less common. These symptoms are usually transient and resolve in 1-2 days despite continuing the drug. So far, there has been no published report on direct comparison between zanamivir and oseltamivir. The current data suggest that both drugs are similar in their efficacy for treatment and prophylaxis. Neuraminidase inhibitors, like M2-channel blockers, require early administration within 48 hours after the onset of symptoms to be effective therapeutically. For both zanamivir and oseltamivir, the reduction in duration of febrile illness is about 1-3 days, which is similar to M2-channel blockers. Neuraminidase inhibitors seem to be a better option for prophylaxis when compared to M2-channel blockers because of its better safety profile and a much lower chance for emergence of drug resistance. A pilot study has been conducted at the Children Cancer Centre, Prince of Wales Hospital, examining the safety profile of oseltamivir as a prophylaxis for influenza in immunocompromised children. The study involved children who were on, or within one year of intense chemotherapy. An 8-week course of oseltamivir at a prophylactic dose was generally well tolerated. Adverse effects, except for mild transient gastrointestinal upsets, were not observed.

In summary, the newer class of antiviral agents for influenza viruses represents a major advance with a better safety profile, broader spectrum of action to cover both influenza A and B, and a much lower chance of emergence of resistance.

Vaccines
The current influenza vaccines are trivalent containing influenza A H1N1, A H3N2, and influenza B. They are inactivated vaccines derived either from partially disrupted virus particles (split vaccines) or from purified enveloped antigens (subunit vaccines). The efficacy of these vaccines depends on the matching between the vaccine strains and the actual circulating strains. The World Health Organization (WHO) maintains a global international surveillance to collect and characterize influenza strains, so as to provide an early warning system for emerging strains with epidemic potential. This network comprises 110 national influenza centers located in 82 countries and 4 WHO collaborating centers for influenza reference and research located in Atlanta, London, Melbourne and Tokyo. WHO issues recommendations for vaccine composition every February for vaccines to be used for the following winter in the northern hemisphere (November to April). Another recommendation is issued every September for vaccines to be used for the following winter in the southern hemisphere (May to September). In Hong Kong, influenza vaccines are offered by the Department of Health/Hospital Authority to the elderly living in residential care home, long stay at-risk patients, and health care workers in contact with these groups. Although, two influenza peaks are observed in Hong Kong, it is more cost-effective to target the major one that occurs in February-March. The Department of Health/Hospital Authority influenza vaccination campaign starts in mid-November of each year.

When vaccine and epidemic strains are closely matched, inactivated influenza virus vaccine offers 80-90% protection against influenza-like illnesses in young healthy individuals. For the elderly, the protection against influenza-like illnesses is much lower (20-30%), but vaccination offers around 40% protection against serious influenza-related morbidity including death. While preliminary data have suggested that the newer anti-influenza agents, neuraminidase inhibitors, could be an effective prophylactic option, however at present, vaccination is still recommended as the primary preventive measure against influenza, and antiviral prophylaxis could be considered as a useful adjunct e.g. for high-risk individuals who have contraindications to vaccination, short-term post-exposure prophylaxis in family or institution.
Origins of Adolescent Medicine
Interest in adolescents within the medical field began in the 1790s. At that time, studies focused only on the biology of adolescence. It was not till 1918 that the first description of a special clinic for adolescents was found in an article entitled “The Work of the Adolescent Clinic of Stanford University Medical School” (Gates). Even in those early days, it was noted that adolescent care demanded attention to the whole person, and not just to particular illnesses. In the 1940’s, the American Academy of Pediatrics first recognized the need for developing Adolescent Medicine as a subspecialty, and believed that paediatricians have a unique role in adolescent health care. The dawn of modern adolescent medicine began in 1951 when the first Adolescent Unit was established in Boston. By 1990, adolescent medicine was well established and received certification as a subspecialty in America. To date, adolescent medicine remains a relatively new paediatric subspecialty in Hong Kong.

Why Adolescent Medicine?
A number of important reasons make specialized knowledge and care of the adolescent necessary. Firstly, physical and psychological characteristics of the adolescents render them different from both children and adults, putting both paediatricians and adult physicians in unfamiliar clinical territory in caring for them medically. Secondly, specific health care needs and psychosocial considerations are typically not well catered for in the traditional paediatric or medical settings. Thirdly, the co-occurrence of physical complaints with psychosocial elements requires the intervention of a multi-disciplinary health care team that includes medical and mental health professionals.

Understanding the Adolescent
WHO defines the adolescent as an individual between 10-19 years of age. Adolescence is a developmental period between childhood and adulthood where rapid changes take place biologically, socially, psychologically, emotionally and intellectually.

It is a time where adolescents face many new life challenges and engage in health-compromising behaviours. It is also a time of opportunity, not just for the adolescent but also for the adolescent health care professionals, to induce change before adverse health consequences or dysfunction result.

Major Developmental Tasks of Adolescence
During this developmental period, adolescents have to achieve certain major developmental tasks. Eventually, they need to (1) integrate new body images, (2) develop independence, (3) be involved in peer group relationships, and (4) form own set of values and a positive self-identity.

In the process, adolescents may find themselves in various quandaries. They may question their own body image: “Am I too fat?”, “Am I too tall?”, “Is my puberty developing normally?” They may confuse self-centred and rebellious behaviour (“I’m a teenager now and I know what I’m doing”) with independent thinking and autonomy. They may refuse to join in family activities, preferring the company of peers whom they regard as more important and more fun to be with. They may confuse sexual desires with “falling in love”, and sexual activity with “becoming an adult”.

It is only after going through a series of learning curves as they mature from early to late adolescence (Table 1) that adolescents ideally establish positive self-identities, body images, peer relationships and true independence.

Some take-home messages in understanding adolescents:
- Each adolescent responds to life’s demands and opportunities in a unique and personal way.
- Time wasting, especially daydreaming, is often a normal part of adolescent development.
- Mild rebellion is common in early and middle adolescence. Marked rebellion, however, may indicate family dysfunction.
- Adolescents often perceive risk-taking behaviours as solutions rather than problems.
- Acting-out behaviours are often a cry for help.
- Adolescent depression can manifest itself as behavioural problems.
- The "perfect" adolescent may possibly be harbouring problematic issues that he or she is trying desperately to deal with.
Approaching Adolescents

In approaching the adolescent, a number of guiding points should be kept in mind. If the adolescent comes with a family member, part of the interview should be given to seeing the adolescent alone, with privacy ensured (no nurses standing around, listening in). The basis of confidentiality should be clearly defined, that is, all issues discussed will be kept confidential between the clinician and the adolescent unless the adolescent is acutely suicidal, acutely homicidal or being abused. The clinician should be unhurried, open, flexible, and ready to listen. These elements will enable a relationship of trust to be established at the outset of the interview.

In interacting with the adolescent, the clinician should be alert to non-verbal cues and provide non-verbal support where necessary. An interactive and non-interrogative style should be used when trying to elicit information from the adolescent. The clinician should adopt a non-judgmental attitude to what the adolescent discloses and yet at the same time, not condone risky behaviours. Beware of adopting a surrogate parent's role and do not start lecturing the adolescent. Watch out for hidden agendas (e.g. the adolescent may present with abdominal pain but in reality is worried about being pregnant).

It is important to remember that in assessing an adolescent, he/she must also be understood in the context of his/her family, school, peers and community participation. The Adolescent Risk Profile Assessment or HEADSS assessment (Goldenring & Cohen 1988, Children's Hospital Los Angeles) is a valuable tool towards this end. "HEADSS" stands for Home, Education (Employment), Activities, Drugs, Sexuality and Suicide. Not only does it provide an opportunity to develop rapport with the adolescent, it also gives the clinician a 'psychosocial biopsy' of the adolescent's situation. It provides the clinician with a clinical impression of the adolescent's risk profile and so acts as a guide to intervention.

In taking the psychosocial history, the clinician should progress from neutral to more sensitive topics. When asking sensitive questions, permission should be sought ("Is it okay if I ask you some personal questions?"). A 'third person' approach should be used for delicate subjects so the adolescent does not feel implicated ("Many adolescents nowadays will take soft drugs. Have you tried it yourself?").

In conducting a physical examination of the adolescent, the clinician should be thorough, gentle and thoughtful. He/she should take measures to protect the adolescent's modesty and privacy, whilst maintaining a friendly and reassuring dialogue and explaining what is being done. Relevant developmental and health matters may be explained during the examination.

Adolescent Health Needs

In order to get a feel for adolescent medicine and the scope of adolescent health needs, here is a list of general diagnostic categories that we see amongst the adolescent clients that we serve at the Adolescent Medical Centre, QEH:

1. Chronic illness and adjustment to chronic illness
2. Somatoform disorders
3. Pubertal disorders

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<thead>
<tr>
<th>Understanding Adolescence</th>
<th>Three Stages</th>
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<tbody>
<tr>
<td>Early (10-13 yr)</td>
<td>Mid (14-16 yr)</td>
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<tr>
<td>Pubertal changes</td>
<td>Make self attractive</td>
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<tr>
<td>‘Am I normal?’</td>
<td>Conflict over independence</td>
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<td>↓ interest in parental activities</td>
<td>Increased experimentation</td>
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<td>Experiment and test limits</td>
<td>Feeling of omnipotence</td>
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<tr>
<td>Same sex peers</td>
<td>Opposite sex peers</td>
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<td></td>
<td>Conform with peer values</td>
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<tr>
<td>Mood swings, daydream</td>
<td>Increased intellectual ability (abstract thinking)</td>
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<tr>
<td>Idealistic vocational goals</td>
<td>Realistic vocational goals</td>
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Table 1.
4. Gynaecological problems
5. Eating disorders
6. Obesity
7. Health-compromising behaviours
8. Destructive self-harm and suicidal attempt
9. Angry outbursts, school refusal, other behavioural and psychological problems
10. Psychiatric illnesses
11. Parent-adolescent relationship problems, severe family problems

**Conclusion**

With increasing recognition of adolescent health needs and of a service gap for adolescents in our current medical setting in Hong Kong, the need for development of adolescent medicine demands our urgent attention. Appropriate and timely management of health issues that adolescents are faced with is vital in ensuring that the health of our upcoming generation is protected and maximized.

**Positive Parenting**

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*Your children are not your children,*
*They are the sons and daughters of Life's longing for itself.*
*They come through you but not from you,*
*And though they are with you they belong not to you.*

*You may give them your love but not your thoughts,*
*For they have their own thoughts.*
*You may house their bodies but not their souls,*
*For their souls dwell in the house of tomorrow, which you cannot visit, not even in your dreams...*  


Parenting has become the central concern when food, vaccines, hygiene are no longer the issues, when children grow healthily, and people are better educated. For today's parents, the questions are: how to optimize their children's potentials and ensure their physical and psychological well beings.

Are paediatricians, as advocates of children, prepared to deliver the services to meet parents’ expectations? And do it professionally? There are many variables which prevent us from being objective. We, in the process of counselling as physicians, suddenly become laymen, not wiser than our patients, and biased by our own values and past experiences.

For parents, parenting is difficult because they themselves are part of the variables that affect parenting. For example, the mismatch between the child's temperament and that of the parents; the parental expectations, be they reasonable or not, unresolved psychological issues that the parents carry over from their past.

However, we, the physicians, and the parents are in the position of power. It is easy to abuse our power if we are unaware of the magnitude of the potential harm that could be done to our children. How to do no harm, at least, or better, how to facilitate the growth of our children has become our new mission in this era.

Positive parenting is a child-centered approach, an approach that recognizes and respects the child's individual variability. It presumes a positive view in life from the parents or the primary care takers, and a belief in the positive nature of human beings; it also presupposes positive reinforcement is the best way of behavioural modification.

The ultimate goal of parenting is to help the children find happiness in life. The parents/ caretakers, through tender, love and care, encourage the development of their children's desirable behaviour, knowledge, interest, responsibility, discipline and independence. In the process of helping them to build a positive self-image, their temperamental traits/ individual variabilities are also put into consideration. Self-image is the corner stone of personal development. We, the physicians, childcare professionals, teachers and parents should at all costs protect our children's self-image so that they will grow with respect and self-confidence, able to love themselves and others, with integrity of personality, able to stand up for their cause, to live up to their potentials, to be reliable and independent, responsible for themselves, their families and society, to uphold their beliefs and principles with dignity. In this context, the children are said to have attained happiness in life.

Raising a child is an ultimate test of the parents’ emotional maturity.

The level of the parents’ emotional maturity, among other factors, can be manifested in different styles of parenting.
There are four different parenting styles: the dismissing parent ignores the child's feelings and does not teach him problem-solving skills; the disapproving parent criticizes the child's emotional expressions, sets rigid limits and regards the child's emotional expressions as manipulation; the laissez-faire parent freely accepts all of the child's emotional expressions, does not set limits and offers little guidance; the emotion coach parent values the child's negative feelings as an opportunity for intimacy, spends time with the child, respects the child's emotion, and never says how the child should feel.

The child of emotion coach parent is more likely to grow with better emotional maturity, to love and to be loved, to have less hassles in life. How to become an emotion coach parent? There are five key steps for emotion coaching: be aware of the child's and the parent's own emotion; recognize the emotion as an opportunity for intimacy and teaching; listen with empathy and validate his feelings; help him verbally label it; sets limits when helping him to solve the problem.

However, it is inappropriate to do emotion coaching when the parent is pressed with time; when the parent is too tired or too upset; when the parent / the child is with someone else; when addressing a serious misbehaviour or when the child is faking.

In the actual coaching, here are principles of parenting suggested by Dr. Dreikurs in his book, *Children: The Challenge* include: encourage the child by avoiding criticism and providing constructive suggestions, encourage him to be self sufficient rather than to become more dependent; the fallacy of punishment and reward; use words which convey to the child that he is in his power to take care of his problems, let him take the natural consequences of his own action; be firm without dominating; show respect for the child and his rights.

A misbehaving child is a discouraged child. It may indicate problems in parenting.

As paediatricians or family doctors, we need to adopt a systematic approach when a child's behavioural or developmental issues are presented. When we develop such an approach, we need to define the behaviour of concern, to check his developmental stages and behavioural style (or temperament) by questionnaires and by interviews, define the concern and parental expectations, clarify the goal, before we reach our preliminary diagnostic impression and our decision for disposition. All of these should be done in the context of the child's family. The following is an example for illustration.

A 9-year-old boy was brought in by his parents because of night terror. He had on and off night terror in the past but recently started to scream and yell one hour after he fell asleep every night for two weeks. He then got up himself and walked around in the house, not communicating to others, mumbling to himself and was at times quiet. He would go back to sleep after a while and would not recall anything happened the next day.

His behaviour of concern was night terror and sleep walking. On examination, he was a soft spoken, quiet and sensitive boy who was developmentally appropriate for his age. The onset of his night terror was associated with his parents who went out late and were called by him several times because he was distressed by being home alone. He believed in supernatural power and was scared to stay home without his parents. The parents appeared to be caring with good relationship. The initial diagnostic impression was night terror and sleepwalking, probably related to stress. Our decision for disposition was, not to wake him up while he was screaming or walking around, to protect the environment so that he would not hurt himself; and quietly lead him back to his bed. Since he was a sensitive boy, any fear could be magnified, therefore his parents were encouraged to communicate with the boy, spend time with him and listen to him about his fear. Parents should review their social activities at night and hold a family meeting to have all members involved in the decision making process so that the boy would feel more in control. The boy was also encouraged to use different means to channel his emotions.

Cases like this are increasingly recognized to be a legitimate area of paediatrics. Behavioral and Developmental Pediatrics (DBP) has become a new subspecialty in American Academy of Pediatrics (AAP) and is an important area in preventive medicine. *It has been shown that early intervention of behavioural and developmental problems reduces unnecessary clinic visits and hospitalization.* It has gained increasing importance in past few years in the United States. It has become a compulsory rotation for paediatric training in many centers; in annual AAP meetings, all important sessions in DBP are allocated with special arrangement.
to facilitate maximal attendance of the audience. Behavioural issues such as feeding, toilet training, sleep, vomiting, biting, temper tantrums, enuresis, nail biting, hair pulling, learning problems, oppositional behaviours, lying, stealing, stuttering, night terrors, etc. are now managed increasingly with evidence-based recommendations and managed in the context of the child's family.

For paediatricians, one of the diagnostic tools for behavioural and developmental assessment is DSM-PC (Diagnostic and Statistical Manual for Primary Care) Child and Adolescent Version, 1996, AAP. Developmental assessment is defined as the assessment of the evolution of new capacities resulting from maturation of our nervous system. A child's behaviours are his actions in relation to adjustment (content of behaviour) and temperament (style of behaviour). DSM-PC provides diagnostic criteria for wider normal variations of different behaviours including developmental variations, behavioral problems and disorders. Its target clients are children of early childhood, middle childhood and adolescence. Therefore DSM-PC is more applicable in Developmental Behavioral Pediatrics than DSM-IV or ICD-10 (The International Statistical Classification of Disease and Related Health Problems).

Positive parenting is an area that seems too soft to pay attention to, but a lot to be pursued.

Books for references:


Recent Advances in the Prenatal Diagnosis of Chromosomal Abnormalities
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Introduction
It is a traumatic experience to many couples to face a baby with major or fatal malformation after a long and painful process of pregnancy and delivery. Chromosomal abnormalities are the most important cause of major fetal abnormalities. Common examples include Trisomy 21, 18, 13, and sex chromosomal aberrations. Most chromosomal abnormalities are non-hereditary and most are more common with increasing maternal age. This article will summarise recent advances in the prenatal diagnosis of chromosomal abnormalities.

Invasive Diagnostic Tests
Amniocentesis is the "standard" diagnostic test for chromosomal abnormalities, usually performed between 16-18 weeks of gestation. Fetal cells are recovered from 15-20 ml of amniotic fluid, cultured and studies. Although it takes 10-14 days for the whole laboratory procedure, fetal karyotyping using this method is most accurate. The major concern of amniocentesis is procedure-related fetal loss, commonly reported to be 0.5 to 1%. The major disadvantage of amniocentesis is that the pregnancy will be 18 weeks or more before the result is available.

Recently, the use of Florescent In-Situ Hybridisation (FISH) and Polymerase Chain Reaction (PCR) have enabled the provision of rapid result in 1-2 days. Both techniques involved the use of chromosome-specific genetic probes to identify the number of a particular chromosomal and therefore are useful for the diagnosis of numerical chromosomal abnormalities. However, there is still concern over its accuracy and therefore the result must always be confirmed by a formal study on post-cultured cells.

Acceptable alternatives to amniocentesis include Chorionic Villus Sampling (CVS) and fetal blood sampling (FBS). CVS is usually performed between 10.5 to 12 weeks of gestations and therefore enables a
much earlier definitive diagnosis. Termination of pregnancy in case of fetal abnormalities will be also safer. However, CVS is technically more demanding and the procedure-related risk is usually quoted to be around 2%, although in our unit the figure is the same as that of amniocentesis. The major advantage of FBS is that it takes only 4-5 days to obtain a full karyotyping study, and therefore is particularly useful in late second trimester. Risk of FBS is much higher, between 2% to 5%. The role of FBS has declined significantly after the availability of FISH and PCR techniques.

Early amniocentesis before 14 weeks of gestation is not acceptable because of the much higher incidence of fetal loss.

Screening Test
Since invasive tests carry a significant risk of fetal loss, they should only be offered to women who are at risk of having chromosomally abnormal babies. Maternal age alone as a screening test is ineffective and could only identify about 35% of chromosomally abnormal pregnancies.

Second trimester biochemical screening test is a well-established effective screening test for Trisomy 21. Common biochemical markers used include Alpha-fetal protein, Human Chorionic Gonadotrophin and Estriol. Based on the maternal serum levels of these markers, after adjusted for gestational age, maternal height, weight and age, it is possible to calculate an estimated risk of Trisomy 21 for that pregnancy. This test is usually performed between 15 to 17 weeks, and amniocentesis will be performed if screened positive. This screening test has a 60-70% of sensitivity in detecting Trisomy 21 pregnancies at a false positive rate of 5%. Currently, the emphasis is to develop a reliable biochemical screening test during first trimester, and the results are encouraging.

Ultrasonography is a non-invasive test and could be used to detect fetal abnormalities. Approximately 30% of Trisomy 21 fetuses have structurally abnormalities, and the incidence is higher with other types of Trisomy. Therefore, karyotyping should always be considered when fetal structural abnormalities, especially if multiple, are detected. Soft markers are ultrasonographic features that are not malformations but fetuses with such soft markers have higher chance of being chromosomally abnormal. Examples of soft markers including mild ventriculomegaly of the cerebral ventricles, mild renal pelvic dilatation, echogenic focus in fetal heart, echogenic bowel, short femur and clinodactyly. In general, the presence of a marker only increases the risk of chromosomal abnormality by about 2 fold. Overall, biochemical screening test is a much more reliable and reproducible screening test.

First trimester nuchal translucency (NT) or nuchal fold thickness measured at 10.5 to 13 week is very effective screening test. NT is a normal finding during early fetal development. However, abnormal babies usually have a thicker NT. If a simple cut-off of 3 mm is used, NT measurement detects 70-80% of chromosomally abnormal pregnancies with a false positive rate of 5%. The major problem of this test is experience and reliability of the operators. The current development centres on the effectiveness of different combinations of biochemical and ultrasound screening tests.

Non-invasive Prenatal Diagnosis
The ultimate goal of prenatal diagnosis is the ability to reach a definitive diagnosis base on fetal genetic materials isolated from maternal circulation, a non-invasive or minimally invasive approach, which carries no risk to the pregnancy. The main obstacle is the difficulty in obtaining a pure fetal sample since less than 0.01% of cells in maternal blood samples is of fetal origin. More recently, it has been shown that maternal plasma has abundant amount of fetal DNA. We have shown that the amount of fetal DNA is higher in pregnancies with Trisomy 21, and correct prenatal diagnosis of single gene diseases have been reported. We have further shown that intact fetal cells are present in maternal plasma which enable the correct non-invasive prenatal diagnosis of Trisomy 21. Although encouraging, there are still many technical difficulties to be solved before non-invasive prenatal diagnosis could be applied for routine clinical practice.

Conclusion
Over the last 2 decades, the major emphasis of prenatal diagnosis has been the development of better and more precise screening tests so as to avoid unnecessary invasive tests and fetal losses. Breakthroughs in medical research in the last 5 years have shown that non-invasive prenatal diagnosis is highly feasible and accurate. It is my belief that in the next decade, the prenatal diagnosis of most genetic diseases will be performed non-invasively.