



History, Risk Factors, Etiology, and Pathogenesis of Down Syndrome

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ABSTRACT

Down syndrome is a congenital genetic disorder caused by abnormalities in the number, structure, or arrangement of chromosome 21 that cause cognitive impairment, congenital malformation, immune disorder, congenital heart disease, and other disorders. It is the most common chromosomal abnormality worldwide. 'Down syndrome' is named in honor of John Langdon Heydon Down, who described its clinical manifestations in an article in 1866. Down syndrome is a congenital genetic disorder caused by abnormalities in the number, structure, or arrangement of chromosome 21 that cause cognitive impairment, congenital malformation, immune disorder, congenital heart disease, and other disorders. It is the most common chromosomal abnormality worldwide. 'Down syndrome' is named in honor of John Langdon Haydon Down, who described its clinical manifestations in an article in 1866. Down syndrome may result from classic trisomy 21, Robertsonian translocation, or chromosomal mosaicism. Maternal age is the most common risk factor, as pathogenesis is linked to biological ovarian aging. Biological ovarian aging may increase the risk of chromosome 21 nondisjunction through hormonal imbalance, depletion of the oocyte pool, impaired cohesion function, oxidative stress, and altered elimination of aneuploid embryos. Knowledge of risk factors and their etiopathogenesis may help recommend an ideal maternal age for pregnancy. A better understanding of these mechanisms may support genetic counseling, pregnancy planning, and appropriate prenatal screening.

Keywords: Down syndrome, etiology, history, pathogenesis, risk factor.



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INTRODUCTION

Down syndrome is a congenital genetic disorder caused by abnormalities in the number, structure, or arrangement of chromosome 21 that cause cognitive impairment, congenital malformation, immune disorder, congenital heart disease, and other disorders.^{1,2} Down syndrome is the most commonly diagnosed chromosomal abnormality. WHO (World Health Organization) estimated that there is 1 Down syndrome birth per 1,000 live births. There are 3000 to 5000 Down syndrome births every year. Currently, there are around 8 million people with Down Syndrome worldwide.² Based on CDC (Centers for Disease Control) data, the incidence of Down syndrome is 1:700 live births.³

Based on Riskesdas (Riset Kesehatan Dasar), Down syndrome cases in Indonesia increased from 2010 (0.12%) to 2013 (0.13%) and to 2018 (0.21%). This genetic abnormality ranks first among congenital disability cases

in Indonesia (0.21%), followed by physical disability (0.16%), speech impairment (0.15%), cleft lip (0.12%), hearing impairment (0.11%), and blindness (0.10%) in 2018.²

MAIN REVIEW

HISTORY

Jean-Étienne Dominique Esquirol first described Down syndrome in a document entitled 'Des Maladies Mentales Considérées Sous les Rapports Médicaux, Hygiéniques et Médico-Légaux' (Mental Illnesses Considered from Medical, Hygienic, and Medico-Legal Aspect) in 1838. This document was the first literature on development and intellectual disability. This disability was called 'idiot' to differentiate from 'insanity'.^{4,5} In 1846, Édouard Séguin published a book titled 'Mental Treatment, Hygiene, and Education of Idiots'. Both works described clinical manifestations of Down syndrome.^{5,6}

In 1866, John Langdon Haydon Down (1828–1896), a British physician, described

Down syndrome in the London Hospital Report. J.L.H. Down, in his article entitled 'Observation on an Ethnic Classification of Idiots', discussed congenital mental abnormality that was called 'mongolism'. This article was the first literature that described complete clinical manifestations of Down syndrome. This abnormality was described as congenital, not as a postnatal injury.^{4,7} J.L.H. Down classified this congenital mental abnormality into types based on ethnicity: Caucasian, Ethiopian, Malay, American, and Mongolian. More than 10% were classified as Mongolian. Physical characteristics of the Mongolian type included a flat, wide, non-prominent face, round cheeks, very narrow palpebral fissures, a wrinkled forehead, big and thick lips, a small nose, yellowish, and less elastic skin. They often suffered from tuberculosis. This abnormality was believed to be inherited hereditarily.⁷

George Edward Shuttleworth (1842–1928) associated older maternal age with

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Down syndrome births for the first time. This observation was written in an article entitled 'Mongolian Imbecility' in 1909. GE. Shuttleworth found that more than 1/3 of 120 total cases of Down syndrome were born from mothers aged > 40 years old when they gave birth; only a small number were born from mothers aged < 30 years. More than half of the children with Down syndrome were born as last-born children in the family.^{4,8}

Jérôme Jean Louis Marie Lejeune (1926–1994), a French pediatrician and geneticist, is known as the discoverer of the cause of mongolism, or Down syndrome. In 1958, Lejeune observed a mongolism or Down syndrome patient in Paris, did chromosomal analysis, and found an extra copy of chromosome 21. Lejeune, with his colleagues Raymond Alexander Turpin and Marthe Gautier, published his discovery in an article entitled 'Les chromosomes humains en culture de tissus' (Human chromosomes in tissue cultures) in 1959. This research showed that mongolism is caused by a chromosomal abnormality, an extra chromosome 21.^{9,10}

The term 'mongolism' has been used to describe Down syndrome for more than a hundred years. In 1961, The Lancet published articles from the 19th century, including JLH Down's. The Lancet urged changing the term of 'mongolism' to 'Langdon-Down anomaly', 'Down syndrome or anomaly', 'congenital acromicria', or 'trisomy 21 anomaly'.¹¹ Lionel Sherples Penronse surveyed 150 families with Down syndrome and found that maternal

age > 35 years is associated with this abnormality.¹² In 1965, Penrose was awarded the 18th World Health Assembly award for his contribution to new knowledge about 'mental subnormality', including mongolism.¹¹ He also demonstrated that some mental disorders did not have a single cause, but a combination of genetic, pathological, and environmental causes.¹²

The People's Republic of Mongolia has been a member of the WHO since 1962. In 1965, Mongolia's delegation informally asked the WHO Director-General to discontinue using 'mongolism' term because it referred to a specific race. After 1965, the terminology was no longer used in WHO publications, but still found in some other scientific literature. The term 'Down syndrome' was used consistently from the early 1970s to the present.^{11,13–14}

Inconsistent 'Down syndrome' terminology is found in the literature and its application in medical education. The terminology of 'Down's syndrome' was used more often than 'Down syndrome' in the early 1960s to mid-1970s. The use of apostrophe s ('s) generally connotes ownership or possession and is inappropriate for naming a disease. Inconsistent terminology complicates scientific literature searches and confuses. In 2004, the WHO style guide recommended not using apostrophe s in diseases.¹⁵ On December 19, 2011, the United Nations (UN) established March 21 as 'World Down Syndrome Day'. The philosophy of this date is related to the etiology of Down syndrome.

The date 21 refers to chromosome 21, and the month of March, or the 3rd month, refers to 3 copies of chromosome 21. World Down Syndrome Day has been celebrated since 2012.^{2,16}

RISK FACTORS

Maternal Age

A mother aged > 35 years old has a higher risk of giving birth to a baby with Down syndrome than a mother. The incidence of Down syndrome in mothers aged > 35 years was 1 per 400 births. In mothers aged < 35 years, the incidence was 1 per 1000 births.¹ In mothers aged 35–39 years old, Down syndrome prevalence was 40 per 10,000 births, aged > 40 years old was 120 per 10,000 births, and aged < 35 years old was 20 per 10,000.^{3,17} **Figure 1** and **Table 1** showed estimated percentage risk of Down syndrome live birth based on maternal age at delivery.^{18–19}

Paternal Age

Fertilization at paternal and maternal ages ≥ 35 years old increased the risk of a baby with Down syndrome. The risk of a baby with Down syndrome increased 6 times in couples aged > 40 years as compared to couples aged < 35 years. If maternal age was < 35 years, paternal age did not affect the risk of Down syndrome birth.²⁰ The number of sperm with abnormal chromosomes increased in older males. About 5%–20% of extra copies of chromosome 21 in Down syndrome result from meiotic failure of paternal gamete cells.²¹

Parity

Higher parity was expected to increase the risk of Down syndrome birth. Results of studies on parity as a risk factor for Down syndrome were varied. Women with higher parity underwent less frequent prenatal genetic screening; lower parity women more often had prenatal genetic screening and tended to terminate pregnancy of Down syndrome fetuses.^{22–23}

Hereditary

One third of chromosome 21 translocation cases, or 1% of total Down syndrome cases, were inherited or called familial Down syndrome. One of the parents of Down syndrome children was a carrier who inherited the chromosome abnormality gene. Carriers did not show clinical manifestations, but could pass the gene to their children. If the

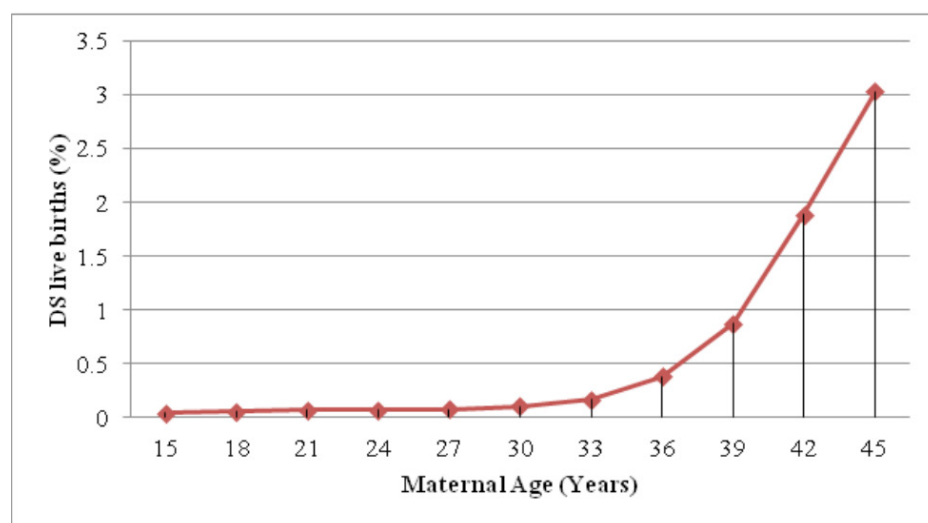


Figure 1. Estimated percentage risk of Down syndrome live-born infant based on maternal age at delivery.^{18–19}

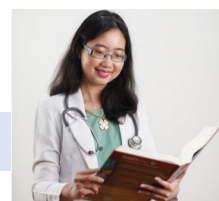


Table 1. Chance of having a live-born baby with Down syndrome according to mother's age at delivery.¹⁸

Mother's Age at Delivery	Chance of Having a Live-born Baby with Down Syndrome	Mother's Age at Delivery	Chance of Having a Live-born Baby with Down syndrome
20–24 years	1 in 1.411	35 years	1 in 338
25 years	1 in 1.383	36 years	1 in 259
26 years	1 in 1.187	37 years	1 in 201
27 years	1 in 1.235	38 years	1 in 162
28 years	1 in 1.147	39 years	1 in 113
29 years	1 in 1.002	40 years	1 in 84
30 years	1 in 959	41 years	1 in 69
31 years	1 in 837	42 years	1 in 52
32 years	1 in 695	43 years	in 37
33 years	1 in 589	44 years	1 in 38
34 years	1 in 430	45 years	1 in 32

father was a carrier, the risk of having a Down syndrome baby was 3% (2%–5%). If the mother was a carrier, the risk of having a Down syndrome baby was 12% (10%–15%).^{24,25}

History of Giving Birth to a Child with Down Syndrome

The risk of a birth with Down syndrome in a woman with a history of delivering a child with this chromosome abnormality was 1:100. Carrier parents and common in translocation of chromosome 21 type caused recurrent Down syndrome births.^{2,24}

Viral Infection

Rubella viral infection disrupts embryogenesis, causes gene mutations, and changes the number and/or structure of normal chromosomes.¹

Exposure of Ionizing Radiation

Women with a history of ionizing radiation exposure have a higher risk of having classic trisomy 21 Down syndrome type. The time of radiation exposure was estimated before the first meiosis phase was completed or around the time of ovulation. Approximately 30% of mothers with children with Down syndrome have been exposed to radiation. The 1986 Chernobyl radioactive nuclear reactor accident in West Berlin caused a temporary cluster of births with chromosomal abnormalities including Down syndrome.^{1,26}

Consanguineous Marriage

Consanguineous marriage increased the risk of classic trisomy 21 Down syndrome type birth. The probability of crossing over two recessive mutant alleles from 2 individuals due to consanguineous marriage increased and caused genetic abnormalities.²⁷

Smoking History

Smoking history during pregnancy increased the risk of Down syndrome. Cigarette smoke contains toxic agents that affect the process of fetal chromosome formation.^{2,28} A study in Japan by Tsuchida A, *et al.*, showed smoking history during pregnancy increased the risk of trisomy births.²⁸ Along with aging, long-term tobacco smoke exposure might be related to degradation of cohesin protein that causes aneuploid oocyte ovulation and increased birth of babies with chromosome number abnormalities.^{28–30} But some previous studies did not show a significant association between maternal smoking and trisomy.^{31,32}

Folic Acid Deficiency

Females with folic acid deficiency had a higher risk of having a classic trisomy 21 Down syndrome type baby. Folic acid has a role in the process of cell division and growth. Folic acid deficiency in oocytes caused hypomethylation and disrupted the meiosis components that are needed during chromosome 21 division.^{33,34}

ETIOLOGY

The etiology of Down syndrome is an abnormality of the structure, number, or location of chromosome 21. Based on the etiology, Down syndrome is classified as classic trisomy 21, translocation, and mosaic.¹

Trisomy 21 Classic

Classic trisomy 21 or non-disjunctional is the most common type of Down syndrome (92.5%). Delayed movement during anaphase lag causes failure of chromosomes to attach to the nucleolus. Failure of chromosome 21 separation causes an extra copy of chromosome 21. This Down syndrome type is not inherited, but the risk of recurrent Down syndrome births in a family is quite high, 1:100 live births. The standard nomenclature of classic trisomy 21 is 47, XX + 21 or 47, XY +21. **Figure 2** showed classic trisomy 21 karyotype.^{1,25,35}

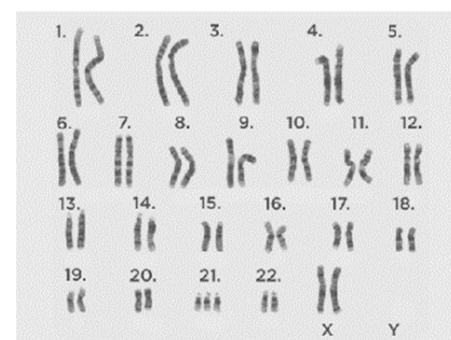


Figure 2. Classic trisomy 21 karyotype.³⁵

Translocation

Translocation or familial Down syndrome occurs in about 4.5% of total cases and can be inherited genetically. Translocation Down syndrome type is Robertsonian translocation, where one chromosome 21 breaks off and attaches to another chromosome. The two long arms (q) of acrocentric chromosomes 13, 14, 15, 21, and 22 fuse with the centromere, and the short arms (p) lose their ribosomal RNA copies. Robertsonian translocations of chromosomes 21 and 14 most often cause Down syndrome. The standard nomenclature of this type is 46,XX,t(14q21q) or 46,XY,t(14q21q). **Figure 3** showed translocation of chromosome 21 and karyotype 14 karyotype.^{1,25,35}



Mosaic

Mosaic or partial trisomy is the rarest type of Down syndrome and occurs in 1%–2% of total cases. People with mosaic Down syndrome have two types of cells: cells with trisomy 21 and cells with normal chromosomes. They are said to have milder clinical manifestations than other Down syndrome types, but in reality, the severity of its clinical manifestations varies. The standard nomenclature of this type is 47, XX+21/46XX or 47, XY+21/46XY.^{1,25,35}

Normal Number of Chromosome Concept

Sperm and ovum cells have 23 chromosomes. The fertilization process forms a zygote with a total of 46 chromosomes that will divide by meiosis. If during the formation process of gamete cells, chromosomes fail to separate perfectly, the cells will have an abnormal number of chromosomes. Fertilization of these gamete cells will form a zygote with chromosomal abnormalities. Failure of chromosome 21 segregation may produce a gamete with an additional copy of chromosome 21. **Figure 4** show normal number of sperm and ovum chromosome.³⁵

Phenotype Manifestations Theory and Health Problems of Down Syndrome

An extra chromosome 21 causes phenotypic consequences and health problems. Two principal hypotheses have been proposed that affect the Down syndrome phenotype: chromosomal instability and the gene dosage effect. Chromosomal instability causes loss of chromosomal balance.^{36,37} Some gene candidates on chromosome 21 are thought

to cause phenotype consequences and health problems in Down syndrome (**Table 2**).²⁴

According to the gene dosage effect, an extra copy of chromosome 21 causes excessive expression of this chromosome in cells and tissues. An extra copy of chromosome 21 at proximal 21q22.3 results in intellectual disability, characteristic facial features, hand anomalies, and congenital heart disease in Down syndrome.^{36,37}

Physiologic Oogenesis and Oocyte Recruitment Process

Ovum formation process, or oogenesis, is divided into 4 phases. The first phase is initiation of mitosis and meiosis commitment, which takes place at 8–10 weeks of pregnancy. The second phase is the formation of follicles, which takes place in the second trimester of pregnancy. The third phase is the growth of oocytes, which begins after entering the age of sexual maturity. Oocyte growth lasts about 85 days, with its peak occurring at ovulation. The fourth phase begins if fertilization occurs.³⁸

The meiosis cycle of oocyte chromosomes is classified into 3 phases: prophase, dictyate arrest, and division. The prophase stage occurs after DNA replication; this process includes homologous chromosomes pairing, synapsis and recombination, and dictyate arrest (diplotene arrest). Oocytes will remain in the diplotene arrest phase until they reach sexual maturity. After reaching reproductive age, the LH hormone will trigger ovulation and

completion of meiosis I in oocytes. Ovulated oocytes will enter the metaphase and anaphase stages of meiosis II. Completion of meiosis II will only occur if the oocyte is fertilized by spermatozoa.³⁸

The oocyte recruitment process is classified into initial recruitment and cyclic recruitment (**Figure 5**). Initial recruitment is the recruitment of primordial follicles to enter the growth phase. This process begins with the formation of follicles. The hormone that plays a role in initial recruitment is not yet known. Other primordial follicles that are not recruited will remain dormant till they enter the growth phase or are depleted. Cyclic recruitment is the recruitment of antral follicles to be ovulated. This process begins since puberty. Antral follicles that are not recruited will undergo apoptosis. The FSH hormone initiates the cyclic recruitment process.³⁹

Figure 6 shows a description of failure of chromosome separation or nondisjunction. Nondisjunction of meiosis I occurs due to the failure of homologous chromosome separation, resulting in 2 gametes with 1 extra chromosome and 2 gametes lacking 1 chromosome. Nondisjunction of meiosis II occurs due to the failure of sister chromatid separation, resulting in 2 gametes with a normal number of chromosomes, 1 gamete with 1 excess chromosome, and 1 gamete with a deficiency of 1 chromosome. Under normal conditions, 4 gametes are produced with a normal number of chromosomes.⁴⁰

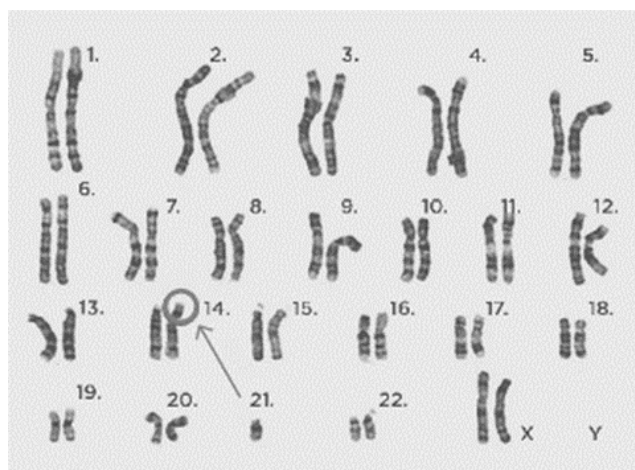


Figure 3. Translocation between chromosome 21 and karyotype 14.³⁵

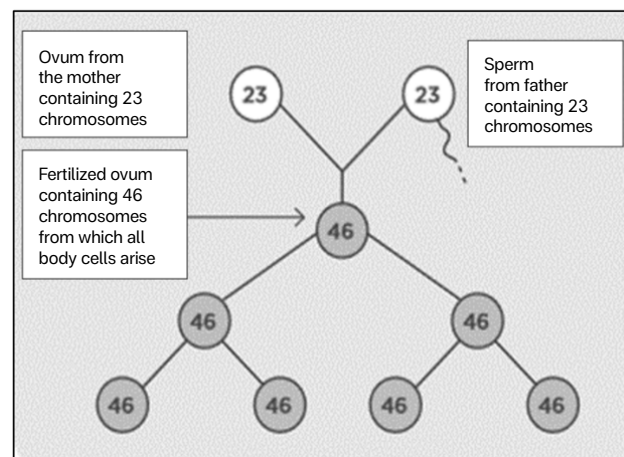


Figure 4. Normal number of sperm and ovum chromosome concept.³⁵

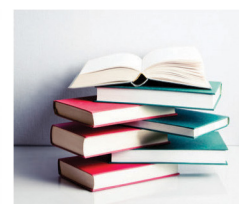
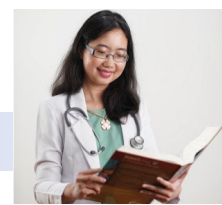


Table 2. Candidate dosage sensitive genes on chromosome 21 that cause Down syndrome phenotype.²⁴

Gene Symbol	Full Name	Location
APP	Amyloid beta (A4) precursor protein	21q21.2, 21q21.3
OLIG1	Oligodendrocyte transcription factor 1	21q22.11
OLIG2	Oligodendrocyte lineage transcription factor 2	21q22.11
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	21q22.13
DSCAM	Down syndrome cell adhesion molecule	21q21.2
SYNJ1	Synaptojanin 1	21q21.2
JAM2	Junctional adhesion molecule 2	21q21.2
SIM2	Single-minded homolog 2 (Drosophila)	21q21.2, 121q2.13
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog	21q21.3
PTTG11P	Pituitary tumor-transforming 1 interacting protein	21q21.3
ADAMTS1	ADAM metalloproteinase with thrombospondin type 1 motif 1	21q21.3
ITSN1	Intersectin 1	21q22.1-21q22.2
SYNJ11	Synaptojanin 11	21q22.2
ETS2	ETS proto-oncogene 2, transcription factor	21q22.3
SLC19A1	Solute carrier family 19 member 1	21q21.3
COL6A1	Collagen type VI alpha 1	21q21.3

PATHOGENESIS

The exact cause of Down syndrome is unknown. It is suspected that several genes are related to Down syndrome births. Advanced maternal age is also associated with this chromosomal abnormality. The hypothesis of 'biological aging', 'genetic aging', hormonal changes, and changes in the mechanism of spontaneous abortion may explain why old age is possibly increasing the risk of having a baby with Down syndrome.^{1,41,42}

Classic trisomy 21 is more associated with maternal age than other types of Down syndrome. Older maternal age is thought to contribute to failure of oocyte separation (nondisjunction/mal-segregation) of chromosome 21. The translocation type of Down syndrome is more associated with the hereditary or de novo origin. In contrast, the mosaic type is thought to occur due to post-zygotic chromosome mitosis failure (mitotic error) in a normal zygote.^{43,44}

Failure of Chromosome 21 Separation

Failure of chromosome 21 separation, or non-disjunction, most often originates from the maternal meiosis I stage of the oocyte. Allen, et al., showed that chromosome non-disjunction most commonly originated from the maternal side (88.73%) and occurred at

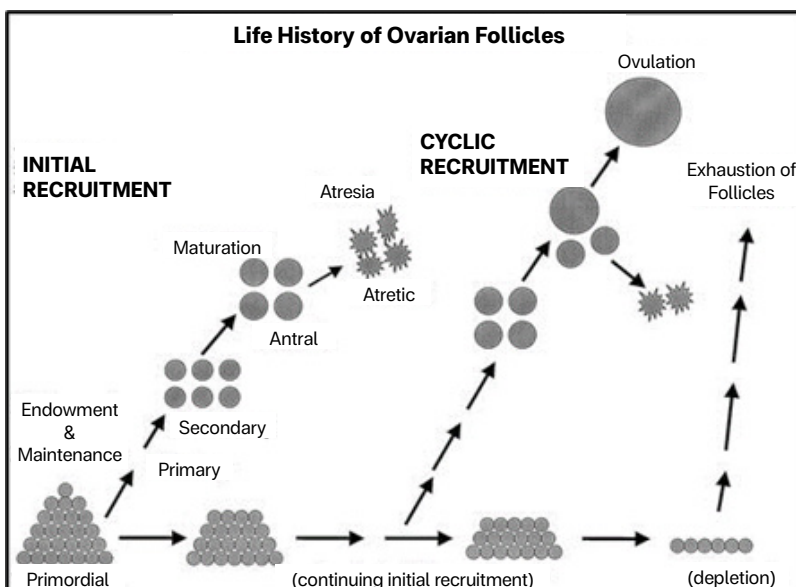


Figure 5. Life history of ovarian follicles.³⁹

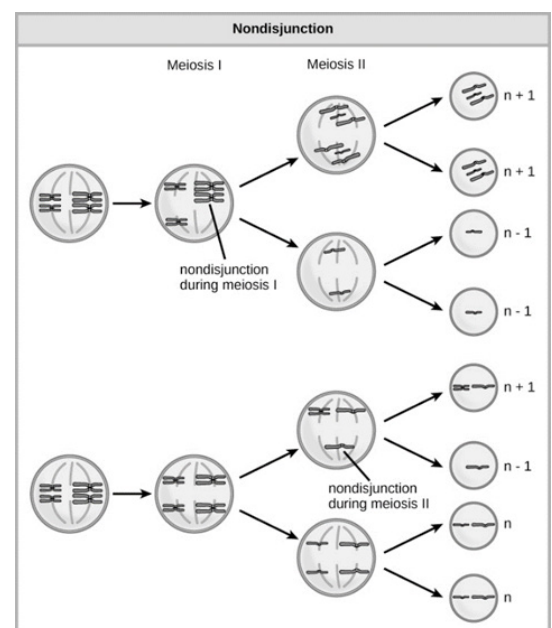


Figure 6. Failure of chromosomal separation or non-disjunctional during meiosis I and meiosis II.³⁹



meiosis I (77.07%) compared with meiosis II (22.9%).⁴⁵ Consistent results were also reported by Ghosh, *et al.*, which states that non-disjunction of chromosome 21 occurred at stages I and II meiosis at 78% and 22%, respectively.⁴⁶ Women's oocytes when aged ≥ 35 years, are more susceptible to chromosome abnormality. According to Oliver, *et al.*, Down syndrome fetuses experience chromosome 21 failure at the meiosis 1 stage (243/615) and meiosis 2 (126/253) in most mothers who are > 34 years old at the time of conception.⁴⁷

Genetic Aging Hypothesis

The genetic aging hypothesis by Brook, *et al.*, explained that mothers of Down syndrome children had an older genetic age than their chronological age. Genetic aging is thought to cause biological aging in the ovaries, which increases the possibility of chromosome separation failure in oocytes (meiosis error).⁴⁸ This hypothesis was challenged by Dorland, *et al.*, and Ghosh, *et al.*, who showed there was no difference in telomere length in mothers of Down syndrome children compared to women with the same chronological age. Telomere length is used as a parameter of genetic age.^{46,49}

Biological Aging Hypothesis

Brook, *et al.*, proposed a biological aging hypothesis for the ovaries. Biological aging of ovaries was thought to increase the possibility of oocyte chromosome meiosis failure and the birth of babies with Down syndrome.⁴⁸ Biological aging of the ovaries is influenced by ovarian hormonal imbalance, limited oocyte pool, decreased ovarian protein degradation, oxidative stress in ovaries, changes in abortion mechanisms, and genetic mutations or abnormalities.⁴⁹

Ovarian Hormonal Imbalance

Hormones play an important role in ovum maturation and the biological aging of the ovaries. FSH (Follicle Stimulating Hormone) levels increase with biological aging of the ovaries. Van Montfrans, *et al.*, found increased FSH levels in mothers of Down syndrome children.⁵⁰ Increased FSH will affect cohesin levels, thereby disrupting the chromosome separation process. Exposure to high levels of FSH will reduce the number of oocytes and increase the susceptibility of aneuploid

oocyte recruitment and cause chromosome number abnormalities.⁵¹

Anti-Mullerian hormone (AMH) predicts ovarian aging and is considered more accurate than a woman's chronological age. AMH acts as a modulator of antral follicle growth and recruitment, regulates the threshold of FSH sensitivity, prevents oocyte degeneration, and follicle atresia. AMH levels decrease with age.^{52–53} Shim, *et al.*, showed that AMH levels in mothers of children with chromosome abnormalities (3.18 ng/mL) were lower than in mothers of children with normal chromosome numbers (3.43 ng/mL).⁵⁴

Limited Oocytes Pool Hypothesis

The limited oocyte pool hypothesis was proposed by Warburton.⁵⁵ Older women will experience a decrease in the number of antral follicles due to hormonal imbalance in the ovaries. Antral follicles are a direct marker of follicle growth at the early stages of the menstrual cycle. They are thought to be closely related to the number of primordial follicles in the ovaries. A decrease in antral follicles increases the possibility of premature oocyte ovulation or post-mature oocytes. This process will increase the possibility of suboptimal and aneuploid oocyte ovulation.^{43,56}

Decrease of Ovarian Protein Degradation

Decreased ovarian protein degradation in old age was suspected to be related to failure of chromosome segregation during meiosis II (meiosis error). Tsutsumi, *et al.*, showed that levels of meiosis-specific cohesin protein subunits, namely REC8 and SMC1B, decreased in women aged 40 years compared with women aged around 20 years ($p < 0.01$).⁵⁷ Decreased cohesin protein degradation and failure of new cohesin production may cause premature sister chromatid rupture. Premature sister chromatid separation was associated with very low cohesin levels, increasing the possibility of ovulation of aneuploid oocytes and the birth of babies with chromosome number abnormalities.^{29,30}

Oxidative Stress

Ovarian biological aging due to oxidative stress may be caused by chronic

inflammation. Chronic inflammation can be caused by smoking, radiation exposure, chemical exposure, and infection, causing mitochondrial dysfunction. Mitochondria have the main role in producing cellular energy and producing reactive oxygen species (ROS). In addition, mitochondria also play a role in regulating steroidogenesis, which affects oogenesis.^{58–60}

Increased intracellular ROS levels due to mitochondrial dysfunction and/or decreased antioxidants will damage DNA, proteins, and lipids, causing oxidative stress. Oxidative stress-induced apoptosis and cell cycle disruption disrupt homeostasis and the processes that maintain the ovaries. Disruption of sex hormone secretion will reduce the quality and viability of oocytes. This process increases the likelihood of aneuploid oocyte ovulation.^{58–60}

Failure of Spontaneous Abortion Mechanism

It was suspected that there was a change in the mechanism of spontaneous abortion of fetuses with chromosomal abnormalities in older mothers. Pregnancy of fetuses with chromosomal abnormalities causes 50%–60% of spontaneous abortion cases.⁴¹ Choi, *et al.*, showed that the number of spontaneous abortions of aneuploid fetuses in mothers aged ≥ 35 years (62/189) was less than in mothers aged < 35 years (127/189).⁶¹ The mechanism of spontaneous abortion in aneuploid fetuses is not yet known. Changes in the mechanism are suspected of increasing the possibility of aneuploid fetuses surviving and being born.⁶²

Maternal Genetic Mutations

Maternal genetic mutations or abnormalities can accelerate ovarian biological aging. Stroom, *et al.*, showed that mothers of children with Down syndrome experience menopause earlier than mothers of children without Down syndrome. The most common cause of early menopause is ovarian failure.⁶³ **Table 3** lists the names, locations, and functions of genes that play a role in protecting the ovaries from biological aging. Mutations or abnormalities in these genes will disrupt ovarian physiology, accelerate the biological aging process of the ovaries, and increase the risk of giving birth to aneuploid babies.^{64,65}

**Table 3.** Genes with known role in protection of the ovaries against aging.^{64,65}

Gene	Location	Function
WNT4	1p36.23-p35.1	Female sex determination and differentiation
FIGLA	2p13.3	Primordial follicle and zona pellucida formation
NOBOX	7q35	Transition from primordial to growing follicles
FOXO3	6q21	Transition from primordial to growing follicles
PTEN	10q23.3	Transition from primordial to growing follicles
FSHR	2p21-p16	Hormone-dependent phase of follicular growth
GPR3	1p36.1-p.35	Maintenance of meiotic arrest until the LH surge
MSH4	1p31	DNA mismatch repair during meiotic recombination
MSH5	6p21.3	DNA mismatch repair during meiotic recombination
PGRMC1	Xq22-q24	Apoptosis of ovarian cells
FOXO1	13q14.1	Granulosa cell function
DMC1	22q13.1	Repair of DNA damage during meiotic divisions

CONCLUSION

Down syndrome is the most commonly diagnosed chromosomal abnormality in the world and ranks first as a cause of birth defects in Indonesia. Various research findings and theories have proposed risk factors and etiopathogenesis of Down syndrome. Maternal age as a risk factor is most often associated with the occurrence of Down syndrome and its pathogenesis through the theory of biological ovarian aging. Other risk factors, such as paternal age, maternal smoking history, and parity,

still require further research. Knowledge of the risk factors and etiopathogenesis of Down syndrome is expected to be used as a consideration in recommending the ideal gestational age for mothers.

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Author Contributions

EZ contributed to data collection, preparation of the draft manuscript and its revision. WI

contributed to manuscript review and editing. All authors reviewed and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

Declaration on the Use of Artificial Intelligence (AI)

The authors affirm that the manuscript was prepared without generative AI or automated text tools, and that all content was developed solely by the authors.

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