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Title: Ontogeny of the human pelvis

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ABSTRACT

The human pelvis has evolved over time into a remarkable structure, optimised into an intricate architecture that transfers the entire load of the upper body into the lower limbs, while also facilitating bipedal movement. The pelvic girdle is composed of two hip bones, os coxae, themselves each formed from the gradual fusion of the ischium, ilium and pubis bones. Unlike the development of the classical long bones, a complex timeline of events must occur in order for the pelvis to arise from the embryonic limb buds. An initial blastemal structure forms from the mesenchyme, with chondrification of this mass leading to the first recognisable elements of the pelvis. Primary ossification centres initiate in utero, followed post-natally by secondary ossification at a range of locations, with these processes not complete until adulthood. This cascade of events can vary between individuals, with recent evidence suggesting that fetal activity can affect the normal development of the pelvis. This review surveys the current literature on the ontogeny of the human pelvis.

1. Introduction

The pelvis connects the axial skeleton to the appendicular skeleton, the primary function of which is transfer of the weight of the upper body into the lower limbs during standing or walking. It performs this function partly by providing attachments for, and withstanding the forces of, some of the most powerful muscles in the body. This strong and rigid structure also serves to protect the organs and tissues of the pelvic region, and some abdominal viscera.

The pelvic girdle consists of two large hip bones, known as the os coxae (see Figure 1). These bones connect with each other anteriorly at the pubic symphysis and articulate posteriorly with the midline sacrum at the sacroiliac joints. This forms the pelvic ring, a stable structure that allows little mobility, thus transferring loads from the trunk to the lower limbs.

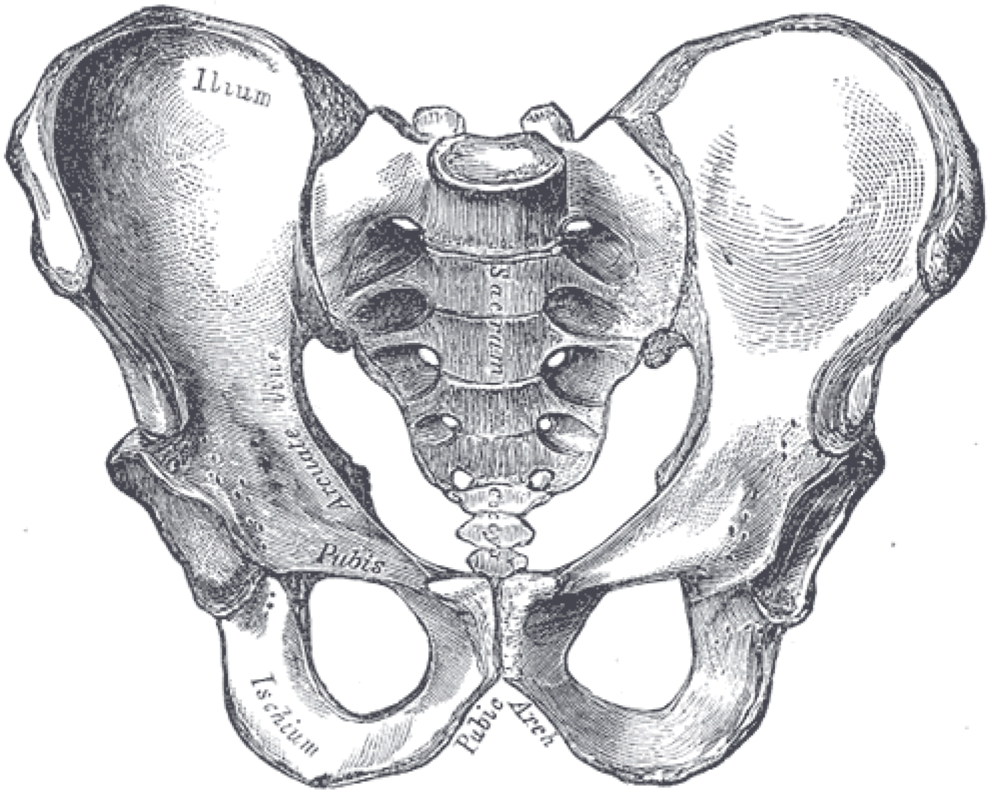

Figure 1: Diagram of the pelvis, articulating with the sacrum of the spine and comprising the left and right hip bones, themselves composed of an ilium, ischium and pubis bone (Gray 1918).

While these pelvic bones are particularly strong and demonstrate structural integrity in the adult human, they are in fact each composed of three smaller bones: the ilium, the ischium and the pubis. Each of these bones develops an intricate three-dimensional form, presenting multiple rami (branches) and fossae (hollows), and establishing complex interfaces with each other. This is exemplified by the triradiate zone, which forms the multi-faceted junction of all three bones at the site of the acetabulum. Interestingly, these individual bones do not completely ossify until well after puberty and as late as 25 years of age, demonstrating the elaborate timeline over which pelvic ontogeny occurs. Indeed, the manner in which this timeline occurs is crucial to the correct formation and ultimate ossification of the bones, and alterations to its intricate organisation can lead to the development of skeletal malformations. This review examines our current knowledge of the development of the hip bones, from initial mesenchymal condensation, through chondrification to ossification, and provides a perspective on future research into the effect of the mechanical environment on development.

2. Morphogenesis of the pelvis

Despite their unique morphology, the pelvic bones follow the same general developmental route as the rest of the skeleton, beginning with the formation of a mesenchymal template, which transforms into cartilage by chondrification, later followed by progressive ossification to form bone. Shape changes continue to occur throughout this process, and developments will be described in each section where relevant.

The pelvis develops from the same mass as the all of the other tissues that form the lower limb, when the prospective skeletal regions of the embryo are composed largely of a loosely organised connective tissue known as mesenchyme. Initially, the lower limb bud begins as a small protuberance in the anterolateral aspect of the body wall at the end of the third intra-uterine week, at the level of the lumbar and first sacral segments (Strayer 1943; Strayer 1971).

The first indication of the development of the pelvis occurs around embryonic day 28, when the lower limb buds begin to develop at the lumbar and upper sacral segments of the embryonic cord (Bardeen and Lewis 1901; O'Rahilly and Gardner 1975). These limb buds initiate as small but rapidly proliferating masses of mesenchymal stem cells surrounded by a layer of ectoderm (the outer border of the embryo) (Laurenson 1964a; O'Rahilly et al. 1956; Yasuda 1973). The obturator, femoral and sciatic nerves rapidly extend deep into the developing limb bud, with their position well established before cells from the mesoderm condense into a core between days 34 and 36 (Laurenson 1963). Therefore, the cells forming the future cartilaginous anlage are forced to organise in a region bounded by these predetermined nerve pathways (Laurenson 1963).

The primordial mesenchyme begins to extend outwards to form three processes: an upper iliac, a lower posterior ischial and a lower anterior pubic (Fazekas and Kósa 1978). The ischial and pubic mesenchymal masses meet to form the obturator foramen, by fusing inferiorly about the position of the obturator nerve. Interaction with the nascent spinal column occurs around days 36 to 38, when the iliac process extends towards the vertebral mesenchymal primordium to fuse with the costal processes of the upper sacral vertebrae (Bardeen 1905; Fazekas and Kósa 1978). Further development eventually leads to the formation of the future pubic symphysis through the meeting of the pubic primordia in the anterior midline (Scheuer and Black 2004).

The sacrum, which articulates with the os coxae and transfers most of the load of the upper body to the hip, emerges as a series of somites or divisions of the mesenchymal notochord, during development of the vertebral column. Somites begin to form near the skull at around 20 days, with three or four subdivisions developing each day such that the five sacral somites appear at about day 29 (Scheuer and Black 2004).

2.1. Chondrification

Chondrification of these blastemal structures begins between intra-uterine weeks 6 and 7 (Bardeen 1905; O'Rahilly and Gardner 1975), with cartilage appearing first in the iliac mass in the region of the acetabulum superior to the greater sciatic notch (Laurenson 1964a). Separated by the course of the obturator nerve, chondrification centres initiate in the pubis and the ischium and are well developed by seven to eight weeks (O'Rahilly and Gardner 1972). Approaching the end of the second intra-uterine month, these three chondrification centres meet and fuse to form a shallow acetabulum, with the ischium and ilium fusing first, followed by a union with the pubic mass (Adair 1918). By the end of the second month, the chondrification of the pubic masses extend to meet and fuse at the midline, at the site of the future pubic symphysis (Adair 1918). At this stage, the anterior superior iliac spine, the ischial spine, and the ischial tuberosity are well defined (Andersen 1962; Bardeen 1905), and thus the cartilaginous pelvis is approaching completion at the beginning of the third intra uterine month (Adair 1918). Chondrification of the sacral vertebrae also commences in the 6^{th} week, with the initiation of up to six chondrification centres in each vertebra. Typically, four sites occur approximately concentrically about the vertebral canal, while two initiate in the centrum on either side of the regressing notochord and later fuse into a single centre as the notochord disappears. Complete fusion into a cartilaginous vertebral body generally occurs in the 4^{th} month (Scheuer and Black 2004).

2.2. Primary Ossification

The pelvis forms through the process of endochondral ossification, whereby chondrocyte cells in cartilage begin to deposit biochemical factors to stimulate mineralisation and blood vessel in-growth. These two steps are essential for bone cells to begin laying down bone in the original cartilage template. This process usually initiates in a specific location for each bone, known as the primary centre of ossification. As the pelvis is composed of three bones, primary ossification commences at an ossification centre in each (see Figure 2), with the timing and location of ossification initiation following that of the prior chondrification process (Laurenson 1964b).

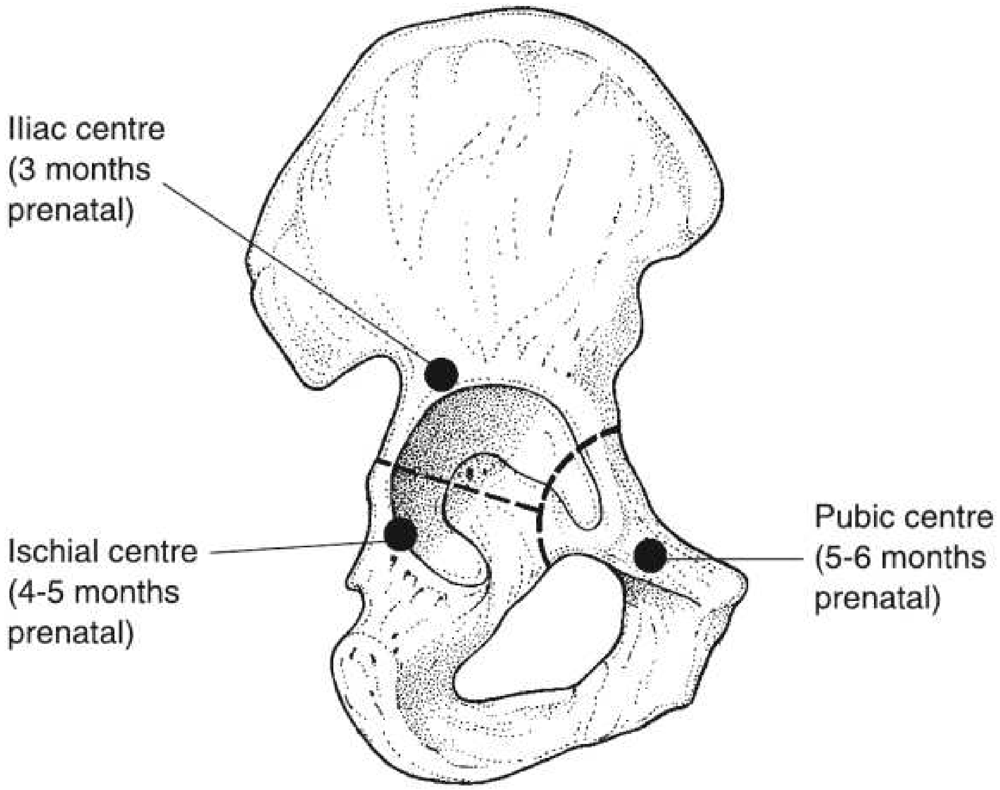

Figure 2: Diagram of the right hip bone, indicating the location of the triradiate cartilage zone (dotted line) that separates the ilium, ischium and pubis bones, and the three primary ossification centres (Scheuer and Black 2004).

2.2.1. Prenatal Primary Ossification

2.2.1.1. Ilium

The first primary centre to develop is in the ilium, appearing around the beginning of the third intra-uterine month. The centre occurs in the perichondrium of the roof of the acetabulum close to the site of the future greater sciatic notch (Laurenson 1964b), close to the foramen of the sciatic nerve. The ossification spreads cranially from this centre, covering the internal and external surfaces of the iliac wing by nine weeks, but without invading the underlying cartilage (a process known as perichondral ossification). Ossification then proceeds by fanning out radially, depositing bone on both an internal and an external shell (Birkner 1978; Delaere et al. 1992; Laurenson 1965). By 10–11 weeks, a primary marrow cavity is formed as pores develop in the ossified shell, allowing osteoblasts and vasculature to invade the internal degenerating cartilage space. The ilium is recognisable by about four to five prenatal months through the presence of the upper border of the greater sciatic notch and the characteristic radiating appearance of the iliac shells.

2.2.1.2. Ischium

In the ischium, the primary ossification centre occurs around 4-5 intra-uterine months and is situated inferoposteriorly to the acetabulum (Laurenson 1963). Perichondral ossification takes place first, followed by expansion through endochondral ossification. The ischium is readily identifiable by the end of the sixth month of pregnancy, having a comma-like appearance that is broader superiorly and tapers inferiorly to the anterior-pointing ramal surface. The superior, posterior and inferior border of the structure are convex in shape, while the anterior border is concave. The inner pelvic surface of the ischium is smooth, while a depression superiorly for the acetabular surface is present on the outer surface.

2.2.1.3. Pubis

The pubic ossification centre appears last, arising between five to six intra-uterine months. It initiates in the superior pubic ramus, anterior to the acetabulum and in close proximity to the passage of both the femoral and obturator nerves. In the early stages of ossification the pubis is reported to be dumb-bell-shaped (Fazekas and Kósa 1978), and is both the smallest and most delicate of the pelvic elements. At this stage, it is composed of two ends, a more rounded lateral (iliac) extremity that points in an infero-oblique direction, and a flatter medial (symphyseal) extremity that extends vertically downwards to compose the body of the pubis.

2.2.1.4. Sacrum

Primary ossification initiates in three locations in each vertebral body of the sacrum; one lateral centre in each neural arch, and one in the centrum. However, ossification centres also develop in the costal elements, which form the ventral aspect of the sacrum and articulate with the auricular surface of the hip bone at the sacro-iliac joint (Schunke 1938). Beginning with the centra of first and second sacral vertebrae in the 3rd prenatal month, all primary ossification centres of the centra and neural arches initiate by the 5th month, with the costal centres appearing between the 6th and 8th month (Scheuer and Black 2004).

2.2.2. Postnatal Primary Ossification

All three primary ossification centres are well developed at birth, and are easily identifiable radiographically. In each of the three bones, the ossification has spread to such an extent that it has formed the bony acetabular wall. These three primary elements demonstrate rapid growth in the first three months after birth, although very little morphological change. This growth then slows noticeably until about three years of age, at which point it becomes even slower. This continues until puberty, at which point a growth spurt is activated as part of the normal secondary sex-related growth changes that occur during adolescence. By the time of birth the ossified region of the ilium presents many of the recognisable features of the mature bone. While the anterior and posterior iliac spines have ossified at this stage, the anterior inferior iliac spine is less well defined (Scheuer and Black 2004).

2.2.2.1. Ilium

Postnatally, while the appearance of the three ossification centres does not change significantly, the cartilaginous acetabular surface undergoes notable changes. At birth, the acetabular surface of the ilium is represented by a slight depression in the centre of the somewhat bulbous inferior extremity. By six months of age, the iliopectineal line can be identified on the ventral rim, and bone is present on the ventral aspect of the future non-articular region of the iliac acetabular fossa by four to five years. By six years of age, a clear line demarcates separation of the articulation sites for the pubis and the ischium, with the immature iliac acetabular extremity taking on a triangular shape. The gluteal margin of this extremity has a scalloped surface, becoming continuous with the anterior border of the ilium passing up towards the anterior inferior iliac spine (Scheuer et al. 2000).

2.2.2.2. Ischium

At birth, the articular acetabular surface of the ischium is located on its posterior lateral surface, as the non-articular acetabular fossa is sited anteriorly. The angles of the articulation sites gradually change with age and by approximately six months of age an angulation develops in the ischium, such that the articulation site for the pubis is found anterior to the superior convex border while the ilium articulates superiorly (Scheuer and Black 2004). By one year of age, the superior border has straightened to the point that the articulation sites are almost perpendicularly arranged about the acetabular fossa, with the ilium articulating superiorly and the pubis anteriorly. Both the ischial spine and superior border project posteriorly and are thickened and well developed by this stage, with the triangular projection of the superior border presenting the future articulation site with the posterior acetabular epiphysis (Scheuer et al. 2000).

2.2.2.3. Pubis

The pubis at birth presents a somewhat oval-shaped articular surface located anteriorly, developing a raised area by six months of age. This elevation develops a metaphyseal border on two sides, allowing for articulation with the ilium superiorly and the ischium inferiorly. The line of demarcation between the articulation sites is first identifiable around three to four years of age, developing more in the approach to ischiopubic fusion. Additionally, the raised acetabular region has flattened by this age.

2.2.2.4. Fusion of Primary Ossification Centres

Fusion between the primary centres first occurs between the ischium and pubis and, although it can begin as early as three years of age, it usually takes place between five and eight years. In the approach to fusion of the cartilaginous joint (synchrondosis) the ends of the joint temporarily grow in size, with this enlargement normally dissipating by ten years of age. Fusion between the ischium and the pubis initially occurs only in the ramal region, with fusion not progressing in the acetabular region until puberty due to the presence of the triradiate cartilage. In the sacrum, fusion of the centres of each neural arch with its associated costal centre occurs between 2 and 5 years postnatally (Scheuer and Black 2004). These centres unite with the centrum centres between years 2 and 6, such that all primary centres have fused by 6 years (Scheuer and Black 2004).

2.3. Secondary Ossification

Secondary ossification centres appear later than the primary ossification centres, usually during the first years of postnatal life. In the pelvis these centres initiate at multiple locations in each of the constituent bones (see Figure 3), with ossification subsequently spreading outward in a similar fashion to the epiphyseal plates of long bones, but in a range of complex patterns. There are generally three main epiphyses that form within the cup-shaped cartilage of the acetabulum, from individual ossicles that form around the acetabular rim, with these eventually expanding to form both the outer rim of the acetabulum and much of the articular surface. An additional secondary centre of ossification for the ilium appears at the iliac crest, whereas the pubic secondary centres initiate at the pubic symphysis and the ramus (as shown in Figure 3). Additional ischial secondary ossification sites occur at the ramus and the tuberosity (as shown in Figure 3), while accessory centres (such as the anterior inferior iliac spine, #6 in Figure 3)) are also known to occur but their initiation sites can be more variable (Scheuer and Black 2004). Much like the end plates of any developing typical long bone, three types of cartilage are represented at each ossification centre in the maturing os coxae: growth, epiphyseal and articular (see Figure 4).

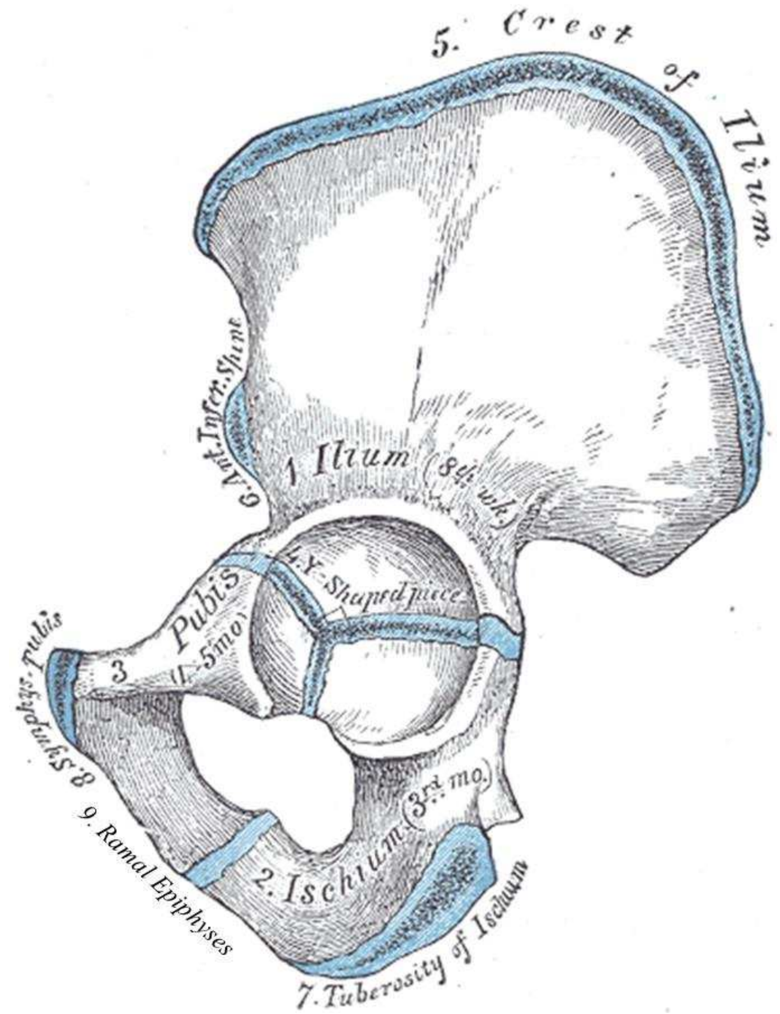

Figure 3: Primary ossification centres of the (1) ilium, (2) ischium and (3) pubis in the left hip bone, and secondary ossification centres (blue) of (4) the triradate cartilage zone, (5) the crest of the ilium, (6) the anterior inferior iliac spine, (7) the tuberosity of the ischium, (8) the symphysis pubis, and (9) the ramal epiphyses. Adapted from (Gray 1918).

2.3.1. Acetabulum

The common secondary ossification feature shared by all three bones of the os coxae is the cartilaginous acetabular anlage. This comprises a socket-shaped area of articular cartilage bordering medially a triradiate unit of growth cartilage between the ilium, ischium and pubis (Harrison 1957; Ponseti 1978a). The articular cartilage lining provides an articular surface for the femoral head at the hip joint, while the triradiate unit comprises regions of growth cartilage contiguous with the bony surfaces and separated from each other by a central region of epiphyseal cartilage. The slow progression of the ossification in this triradiate zone allows the acetabulum to expand during childhood to accommodate the enlarging femoral head (Harrison 1961).

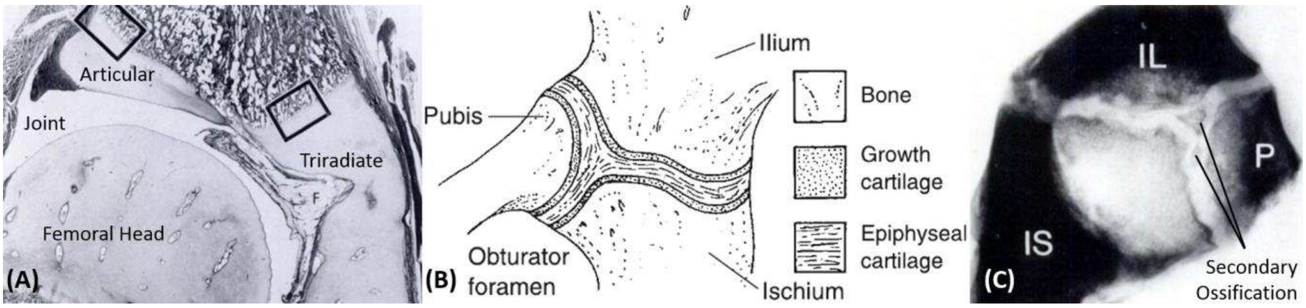

Figure 4: (A) Section through a hip joint of a full term infant (Ponseti 1978a), displaying the femoral head, articular cartilage and triradiate cartilage, with the black rectangles indicating (B) areas of growth and epiphyseal cartilage as ossification of the bone progresses (Scheuer and Black 2004), and (C) a roentgenogram of the acetabulum of a nine-year-old female displaying secondary ossification centres in the triradiate cartilage between the ilium (IL), ischium (IS) and pubis (P) (Ponseti 1978a).

As each of the three secondary ossification centres enlarge they ultimately meet with the ossifying triradiate epiphysis and fusion occurs. The first acetabular epiphysis to ossify is the os acetabuli (anterior acetabular epiphysis), which initiates between nine and ten years of age as a triangular-shaped bone between the pubis and the ilium, as seen in Figure 4C (Ponseti

1978a; Zander 1943). A second acetabular epiphysis arises around 10–11 years of age at the junction between the ilium and the ischium. A third superior epiphysis appears between 12 and 14 years of age, forming a substantial part of the upper rim and roof of the acetabular articular surface. Complete fusion of the triradiate cartilage normal occurs by mid-puberty (11–15 years in females 14–17 years in males), with the pelvic surface generally fusing before the acetabular aspect (Flecker 1932; Freedman 1934; Stevenson 1924).

2.3.2. Ilium

The order of initiation of the other secondary epiphyses after the fusion of the triradiate zone is generally reported to be – from first to last – anterior inferior iliac spine, iliac crest, ischial tuberosity and pubic symphysis. The epiphysis for the anterior inferior iliac spine commences ossification around 10–13 years of age and fuses by around 20 years (Francis 1940), and it has been reported that the ossification of this centre can occur either in isolation, or from an extension of the centre of the superior epiphysis of the os acetabuli (Scheuer and Black 2004). The iliac crest epiphysis comprises two separate ossification centres, with an anterior epiphysis forming the anterior superior iliac spine and the anterior half of the iliac crest, while the posterior epiphysis develops into the posterior superior iliac spine and the posterior half of the iliac crest (Stevenson 1924). The two epiphyses meet in the middle of the crest just posterior to its highest point, following a spiral growth pattern (Birkner 1978). The crest begins to ossify around 12–13 years of age in females and 14–15 years in males, with union of the two ossification centres occurring around 15–18 years in females and 17–20 years in males (McKern and Stewart 1957).

2.3.3. Ischium

The ossification of the ischial epiphysis initiates as a small centre in the ischial tuberosity between 13–16 years of age, commencing union at the superior rim of the epiphyseal surface. This epiphysis then spreads across the surface of the tuberosity, continuing along the ischial ramus as the thin, tongue-like ramal epiphysis (Scheuer and Black 2004). The pelvic surface of the tuberal epiphysis commences union with fusion occurring between 16 and 18 years of age, while the ramal epiphysis has usually reached half way along the ischial ramus by around 19–20 years of age. The ramal epiphysis progresses slowly, with complete union anywhere between 20 and 23 years of age (Scheuer and Black 2004).

2.3.4. Pubis

Morphogenesis at the pubic symphyseal face occurs in two distinct regions, known as the ventral and dorsal demifaces (McKern and Stewart 1957). Its secondary ossification follows a complex pattern, commencing with a type of pre-epiphyseal stage (Meindl et al. 1985), typified by a discernible ridge-and-furrow appearance of the joint surface. No build-up of bone occurs, joint surfaces are not well-defined, and the pubic tubercle displays no evidence of an epiphysis (Scheuer and Black 2004). This morphological appearance does not change up to approximately 20 years of age. Around this time bone begins to be laid directly onto the dorsal face by gradual accretion, having the effect of smoothing over the ridge-and-furrow surface between 15 and 23 years of age (Katz and Suchey 1986). The delimitation of the extremities of the pubic symphysis commences between 23–27 years of age, with the inferior extremity usually initiating before the superior extremity (Todd 1920). These upper and lower extremities generally begin to fuse between 24 and 35 years of age, although it is often not completed until 35 years and indeed may not complete at all (Scheuer and Black 2004).

2.3.5. Sacrum

Each sacral segment remains separate until puberty, with secondary ossification of the sacrum beginning around 12 years. In contrast to the primary ossification pattern of the vertebrae, the secondary ossification of the costal elements begins between the caudal sacral vertebrae, with the S1 vertebra being the last to fuse at the end of puberty (15-16 years). The annular epiphyses between the vertebral bodies similarly commence in a caudocranial direction, with fusion of all epiphyses by 20-25 years (Scheuer and Black 2004). The epiphysis of the sacro-iliac joint develops from discrete ossific islands that appear between 15 and 16 years, with complete union at this surface occurring after 18 years of age (Scheuer and Black 2004).

2.4. Sexual Dimorphism

2.4.1. Prenatal Sexual Dimorphism

Of particular interest to researchers has been sex differences in the immature pelvis. Indeed, the adult pelvis is an area of the human skeleton that displays some of the greatest levels of sexual dimorphism; so much so that the hip bone is often the preferred bone for accurate prediction of sex in adult forensic specimens (Bruzek 2002). While there is a great deal of literature investigating sex differences in the fetal and juvenile pelvis (Correia et al. 2005; Holcomb and Konigsberg 1995; Schutkowski 1993), it is still generally held that though dimorphism may exist from an early age, differences significant enough to permit determination of sex do not occur until the onset of puberty (Scheuer and Black 2004). However, in studies which have reported sex differences in fetal hip bones, the differences tend to parallel those in the adult pelvis. Hromada (Hromada 1939) reported differences in the proportions of the sciatic notch, ilium, and pelvic inlet and outlets, and also identified two main growth phases in the fetal pelvis, with the first ending in no identifiable sex differences at two months gestational age, and the second initiating at seven months with growing indications of sexual dimorphism approaching birth (Hromada 1939). Similarly, Boucher (Boucher 1957) and later Holcomb and Kongsberg (Holcomb and Konigsberg 1995) observed some sexual dimorphism with regard to shape, specifically in the sciatic notch. In contrast, Weaver found no differences in any of the previously proposed measurements, or in new ones devised for the study (Weaver 1980). Furthermore, a recent study used reconstructed CT images of fetal ilia to conduct the first three-dimensional morphometric analysis, with this highly detailed analysis reporting no difference between the sexes (Mokrane et al. 2013). Therefore, while it remains unclear whether significant sexual dimorphism is present prenatally, there is a consensus that any differences are not of a sufficiently high level to reliably determine sex from the hip bone.

2.4.2. Postnatal Sexual Dimorphism

The most comprehensive measurements of sexual dimorphism in the whole pelvis were taken using radiogrammetry of male and female 8- and 18-year-olds, with the only differences detected at 8 years in the breadth of the ischium and acetabular regions (LaVelle 1995). However, males showed significantly greater growth in the acetabulum during puberty, while females presented differentially greater growth in the pelvic cavity (LaVelle 1995).

Most other studies of postnatal sexual dimorphism have focused on the ilium, initially using a metric technique to fit growth curves to iliac dimensions, and finding that the iliac height is the best measure for sex determination (Rissech and Malgosa 2005). More recently, geometric morphometry of multi-slice CT scans has been used to attempt to separate the effects of shape (development) and size (growth) (Bilfeld et al. 2013). They found that, while size does not vary between the sexes, ilium shape becomes sexually dimorphic at 11 years (Bilfeld et al. 2013). However, the trajectories of size and shape do vary throughout ontogeny and between the sexes (Bilfeld et al. 2013). Most recently, a comprehensive geometric morphometric study of photographic data confirmed these findings, and furthermore found that the ontogeny of size and shape are defined by non-linear trajectories that differ between the sexes, and that the rate of maturation of these traits is typically higher in males than in females (Wilson et al. 2015). However, while pelvic growth trajectories in females between puberty and 25–30 years develop to provide larger obstetrically relevant dimensions (i.e. width of the pelvic inlet and outlet), it has also been shown that a reduction in these dimensions occurs from 40 years onwards on a trajectory similar to that of males (Huseynov et al. 2016).

2.5. Congenital and developmental abnormalities of the pelvis

It is obvious from the length and complexity of the ontogenetic timeline described herein that the correct progression of morphogenesis and tissue differentiation is vital to obtaining a complete, functional pelvic girdle.

The most common congenital abnormality of the pelvis is developmental dysplasia of the hip (DDH), which is a dislocation of the femur that results in malformations of both the femoral head and the acetabulum. While it is the femur that dislocates in these cases, evidence exists that there is a relationship between the development of the acetabulum and DDH, with the acetabular cartilage presenting bulges of degraded cartilage on the articular surface in DDH cases (Ponseti 1978b). Additionally, it is known that the presence and sphericity of the femoral head is necessary for the correct development of the acetabulum (Ponseti 1978b). Furthermore, researchers using both ultrasonography and radiography have identified delayed maturation, and the development of a notch near the sclerotic nerve, in the acetabulum in cases of hip dysplasia (Portinaro et al. 1994; Portinaro et al. 1997), again demonstrating a link with structural changes to the pelvis.

3. Mechanobiological influences on pelvic development

While the native adaptation of bone to mechanical loading has been apparent to researchers for more than a century (Frost 1990a; Frost 1990b; Parfitt 1994; Wolff 1892), with deformities such as femoroacetabular impingement thought to occur due to mechanoadaptation in the pelvis of young professional athletes (Matheney et al. 2013; Philippon et al. 2007), evidence of this occurrence in the immature pelvis is less clear. The ilium appears to be most affected, with the characteristic concavities and convexities of the iliac crest not appearing until around two years of age, approximately the time that upright locomotion begins (Scheuer and Black 2004). It has also been proposed that during primary ossification of the ilium in utero, the external shell that forms is thicker than the inner shell due to the action of the gluteal muscles (Delaere and Dhem 1999; Delaere et al. 1992), as shown in Figure 5. Similarly, it has been observed that the internal organisation patterns in early fetal and neonatal trabecular bone in the pelvic ilium bear striking similarities to adult trabecular patterns (Cunningham and Black 2009). As these patterns have been associated with bipedal locomotion in adults, this suggests that the action of in utero limb movements, despite not being weight-bearing, may be sufficient to initiate skeletal remodelling (Cunningham and Black 2009). Furthermore, evidence of high intracortical remodelling activity in both the internal and external cortex of the ilium, which decreases significantly with age, possibly suggests a greater adaptive capability in the infant ilium (Rauch et al. 2007). In contrast, a recent study of ontogenetic changes in the trabecular architecture of the ilium of modern humans posited that the direction of growth was more likely due to genetic or epigenetic factors (Abel and Macho 2011). However, the same study found significant trabecular alignment along the sacro-pubic trabecular bundle in infants, which constitutes the main line of force transmission from the auricular surface to the acetabulum, indicating potential mechanoadaptation (Abel and Macho 2011).

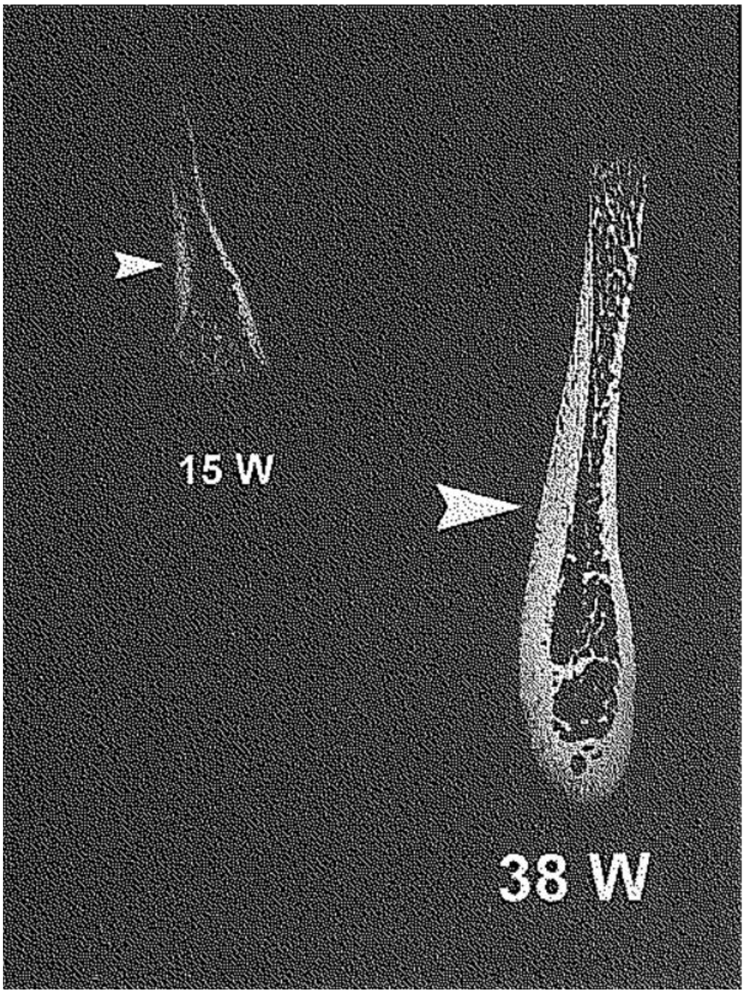

Figure 5: Microradiograph of a frontal section through the right prenatal ilium at 15 weeks and 38 weeks of gestation (Delaere and Dhem 1999). The lateral iliac cortex (arrow) is thicker than the medial cortex at the later gestational age, indicative of mechanobiological response to the action of the gluteal muscles on the lateral surface.

As studies of human pelvic development are exclusively observational, researchers have turned to animal models in an attempt to delineate the effects of prenatal mechanical stimulation as developmental cues. A series of experiments on rat models investigated the effect of mechanical interference on the growth rate and maturation of the acetabulum and sacro-iliac joint (Harrison 1958a; Harrison 1958b). They determined that the correct development of the sacro-iliac joint depends on the integrity of surrounding cartilage and ligaments, while the presence of a femoral head at the acetabulum was found to be necessary to prevent dysplasia (Harrison 1958a; Harrison 1961). Rat models have also been employed to investigate the effects of limb restraint on pelvic development, which led to decreased acetabular surface smoothness that could be partially reversed with the removal of restraint (Hashimoto et al. 2002). Additionally, experimentally induced premature fusion of the triradiate cartilage was found to cause acetabular dysplasia and hip dislocation in rabbit embryos (Gepstein et al. 1984).

Using the embryonic chick model, it has been shown that amputation of the hindlimb bud will prevent the formation of the pelvis (Malashichev et al. 2005; Malashichev et al. 2008), and the importance of mechanical stimulation due to prenatal movements for development of the hip joint was demonstrated in the embryonic chick, with pharmacological immobilization resulting in abnormal orientation of the pelvis and malformation of the acetabulum (Nowlan et al. 2014).

Recent forays into the field of computational biomechanics have provided an alternative avenue of enquiry for developmental mechanobiology, with the potential of replicating the womb environment in silico. Computational studies have allowed for the development of mechanobiological models of hip joint development (Giorgi et al. 2014; Shefelbine and Carter 2004), predicting the development of a malformed acetabulum, decreased acetabular coverage and the development of coxa valga from idealised geometries, under reduced and abnormal movement patterns (Giorgi et al. 2015; Shefelbine and Carter 2004). The biomechanics of human fetal movements has also been investigated computationally, using kicking motions captured from cine-MRI data to determine the intramuscular forces generated at the hip joint during fetal kicking (Verbruggen et al. 2016). However, to date these models either use simplified or adult bone geometries, and cannot fully predict the mechanobiological response that occurs in utero. Further work in this field and advances in imaging techniques will improve the predictive power of these models, and provide a useful tool to investigate development in utero.

4. Conclusion and Future Perspective

The literature summarised here describes over a century's worth of studies of the complex cascade of events that lead to the development of the mature pelvis, one of the most intricately-shaped and important load-bearing bones in the human skeleton. For the most part, this field of study has comprised careful documentation of anatomical specimens from prenatal humans. Investigations using animal models have shed light on the importance of mechanical stimulation in the ontogeny of the pelvis, with more recent advances in medical imaging and computational modelling techniques further elucidating these mechanobiological links. As additional technological strides are made, it may become possible to monitor the development of the pelvis in high resolution, and in real time, and thus further advance our understanding of the ontogeny of the human pelvis.

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Chondrification	Week 5	Blastemal structures of the pelvis have formed from primordial mesenchyme (Bardeen, 1905)
Chondrification	6-7	Chondrification begins in iliac mass (O'Rahilly and Gardner, 1975)
Chondrification	7-8	Chondrification centres initiate in ischial and pubic masses (Gardner and O'Rahilly, 1972)
Chondrification	Month 2	Chondrification centres meet, fuse to form immature acetabulum and pubic symphysis (Adair, 1918)
Chondrification / Primary Ossification	2-3	Ilium ossification initiates (Laurenson, 1964b)
Chondrification / Primary Ossification	3	Cartilaginous pelvis complete (Adair, 1918)
Primary Ossification	4-5	Ischium ossification commences (Laurenson, 1963), ilium is identifiable (Scheuer and Black, 2004)
Primary Ossification	6	Ilium prominence of the iliopectineal line has developed (Scheuer and Black, 2004)
Primary Ossification	6-8	Pubis commences ossification, all three primary bony components present (Sheuer and Black, 2004)
	Birth	
Primary Ossification	Year 1	Ischial spine, pubic tubercle and crest have developed (Scheuer and Black, 2004)
Primary Ossification	2	Anterior border of ilium has bent forwards (Scheuer and Black, 2004)
Primary Ossification	3-4	Iliac and ischial articulation sites on the pubis are clearly demarcated (Scheuer and Black, 2000)
Primary Ossification	4-5	Non-articular acetabular area clearly defined on the ilium (Scheuer and Black, 2000)
Primary Ossification	5-6	Pubic non-articular acetabular area is clearly defined (Scheuer and Black, 2004)
Primary Ossification	5-8	Fusion occurs at the ischiopubic rami (Fazekas and Kósa, 1978)
Secondary Ossification	9-10	Os acetabuli is identifiable, ossific islands occur in triradiate cartilage (Zander, 1943)
Secondary Ossification	10-11	Ossification initiates in posterior acetabular epiphysis (Zander, 1943)
Secondary Ossification	10-13	Ossification centre develops in the anterior inferior iliac spine (Francis, 1940)
Secondary Ossification	11-15	Fusion of acetabulum in females (Stevenson, 1924; Freedman, 1934)
Secondary Ossification	12-14	Superior acetabular epiphysis appears; ossification of iliac crest in females (Stevenson, 1924)
Secondary Ossification	13-16	Ischial epiphysis commences ossification (Francis, 1940)
Secondary Ossification	14-17	Fusion of acetabulum and ossification of iliac crest in males (Stevenson, 1924; Freedman, 1934)
Secondary Ossification	15-23	Smoothing of dorsal plateau of pubic symphysis (Katz and Suchey, 1986)
Secondary Ossification	16-18	Ischial tuberosity has developed fully (Scheuer and Black, 2004)
Secondary Ossification	17-20	Fusion of Iliac crest epiphyses begins (McKern and Stuart, 1957)
Secondary Ossification	19-20	Ischial epiphysis extends half way along the ramus (Scheuer and Black, 2004)
Secondary Ossification	20	Complete fusion of the anterior inferior iliac spine (Francis, 1940)
Secondary Ossification	20-23	Ischial epiphysis, iliac crest have completed union (McKern and Stuart, 1957)
Secondary Ossification	23-27	Pubic tubercle epiphysis, inferior and superior borders delineated (Todd, 1920)
Secondary Ossification	24-30	Smoothing of ventral and dorsal pubic symphysis (Todd, 1920)
Secondary Ossification	35	Ventral rampart is complete and the symphyseal rim is mature (Todd, 1920)

Figure 6: Timeline of chondrification and ossification events in the ontogenic development of the human pelvis

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